Supplementary information for:

Synthesis of Bacteriopheophytin *a*

Duy T. M. Chung, Khiem Chau Nguyen,† Yizhou Liu, and Jonathan S. Lindsey*

†Deceased

Department of Chemistry
North Carolina State University
Raleigh, NC 27695-8204 USA

Table of Contents **Page number**

I. Experimental Section

Reagents and solvents. All chemicals from commercial sources were used as received. Distillation of diethyl ether or THF was carried out over sodium/benzophenone ketyl under argon. Anhydrous acetonitrile, dichloromethane, DMF, DMSO, and methanol were purchased from commercial sources and used as obtained. Reagent-grade diethyl ether contained butylated hydroxytoluene as an inhibitor. Acetonitrile for absorption spectroscopy was HPLC grade. All other solvents were reagent grade from commercial suppliers. Degassed solvents employed in inert-atmosphere reactions were prepared by bubbling with argon within 1 h prior to their use. Water for reaction workup and extractions was deionized.

Silica. Silica for column chromatography (230–400 mesh, 60 Å) was obtained from Silicycle Inc. In some cases, silica was deactivated in the following way: a quantity of silica was treated with hexanes containing 1% triethylamines (v/v) to afford a slurry, which was then concentrated to dryness under reduced pressure. The resulting deactivate silica was used in some column chromatography procedures.

Known compounds. Known pyrroles **9** (pre-A)[28] and **20** (pre-C)[27] were prepared as described in the literature. Compounds **19**, **21**, and **22** are known[30] but were prepared here by new or streamlined procedures. Compound **8** where R = phytyl has been prepared by a different route.

Native pigments. Native **BChl *a*** was obtained from Frontier Specialty Chemicals. Demetalation of **BChl *a*** with TFA following a reported procedure[82] and purification by chromatography [RP-C_{18} silica, THF/H_2O (7:3)] gave native-derived **Bpheo *a***.

Chiral HPLC analyses – Michael additions. Analysis by chiral HPLC (normal phase) was carried out using a Chiralpak IC, a column temperature of 25 °C, a flowrate = 1 mL/min, and an analyte concentration (in hexanes) of 1 mg/mL. The reactions with propanal (Fig. 3, left panel) used *i*PrOH:hexanes = 7:93 and λ_{det} = 202±4 nm, whereas the reactions with butanal (Fig. 3, right panel) used *i*PrOH:hexanes = 10:90 and λ_{det} = 204±4 nm.

Reaction monitoring. Due to the formation of increased conjugation in the products, both Paal-Knorr-like reaction and IBX oxidation could be easily monitored by absorption spectroscopy[30] (Fig. S7).

Conversion of **11** → **12**. Aliquots (1.0 μL) were removed from the reaction mixture ([**11**] = 0.087 M initially), diluted with 3.00 g of acetonitrile, and analyzed in a 1-cm pathlength cuvette by absorption spectroscopy.

Conversion of **12** → **13**. Aliquots (1.0 μL) were removed from the reaction mixture ([**12**] = 0.1 M initially), diluted with 3.00 g acetonitrile, and analyzed in a 1-cm pathlength cuvette by absorption spectroscopy.

RP-HPLC analyses – macrocycles. Analysis was carried out via reversed-phase (non-chiral) HPLC using a Shim-pack XR-ODS column (2.2 μm, 3.0 x 50 mm), a column temperature of 40 °C, a flowrate of 0.5 mL/min, injection volume of 5 μL; the void volume was ~0.8 minutes. The solvents A (water with 0.1% formic acid) and B (acetonitrile with 0.1% formic acid) were used in a gradient: 7 min (5% of B to 95% of B), 7 min (95% of B) and 2 min (5% of B). Detection was achieved online by absorption spectroscopy at specified wavelengths (see text) and/or by mass spectrometry. The data are shown in Figs. 5C, 6D, S13, S15 panel A, S16 panel A, S21.

Measurements of optical activity. Analysis was carried out using a Jasco P-2000 Polarimeter in a 10-cm pathlength quartz cuvette.

MALDI-MS analyses. The free base macrocycles were analyzed using α-cyano-4-hydroxycinnamic acid (CHCA) whereas the magnesium chelate **BChl *a*** was analyzed using the matrix pioneered by Calvano and coworkers,[88] 1,5-diaminonapthalene (DAN).

Absorption spectral analyses. The absorption spectra of the macrocycles were collected in freshly distilled diethyl ether and were assessed for the ratio of the intensity of the Q_y band and the maximum of the B bands (I_{Qy}/I_B),[83] a longstanding metric, initially used to assess purity of native samples but now also used for fundamental spectroscopic comparisons.

Determination of molar absorption coefficients. Values of the molar absorption coefficient were determined for selected compounds including dihydrodipyrrin **22**, Knoevenagel enone **23**, and bacteriopheophorbide **24**. The quantity of material employed, dilution procedure, and resulting spectra (Figs. S26, S27, and S28, respectively) are provided in section X1.

Handling of oxidation-sensitive compounds. Synthesis and handling of all dihydrodipyrrins (**12**, **13**, **22**), Knoevenagel enone (**23**), and macrocycles (**24** and onward) were carried out with use of anaerobic conditions, very dim ambient lighting, and limited use of normal-phase chromatography. The formation and handling of the macrocycles was done in near-darkness. The Pd-mediated hydrations were very sensitive to the presence of oxygen; therefore, the solvents were carefully degassed by four freeze-pump-thaw cycles, and the reaction was carried out under an argon atmosphere.

SCXRD Analyses. For each of the three compounds, the diffraction data were collected at 100 K using a Bruker D8 Venture diffractometer (CuKα, 1.54178 Å) equipped with APEX5[S1] software. The crystal structure was calculated, integrated, and processed using SAINT,[S2] SHELXL,[S3] and OLEX2[S4] software. All calculations for crystallographic distances and angles were analyzed by OLEX2 software. The crystallographic information file (CIF) for pyrrolidine **5** (CCDC 2519172; Flack parameter: -0.006(19)), pentynamide **16a** (CCDC 2519171; Flack parameter: 0.09(4)), and pentynamide **16b** (CCDC 2519170; Flack parameter: -0.10(19)) and can be retrieved at www.ccdc.cam.ac.uk.

2-(Trimethylsilyl)ethyl *(E)*-5-nitropent-4-enoate (1). Following a reported procedure[34] with modifications, a solution of succinic anhydride (100.07 g, 1.0000 mol), 2-(trimethylsilyl)ethanol (130.00 g, 1.0994 mol) and 4-dimethylaminopyridine (24.40 g, 0.1997 mol) in CH_2Cl_2 (750 mL) was cooled to 0 °C (ice-water bath) and treated dropwise with triethylamine (155 mL, 2.11 mol). The resulting mixture was allowed to warm to room temperature and was then heated overnight at reflux. The reaction was quenched by the slow addition of a solution of aqueous HCl (3 M, 1 L). The mixture was allowed to stir for 30 min at

room temperature. The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2 (500 mL x 3). The combined organic extract was dried over Na_2SO_4 and concentrated under vacuum to afford the succinic acid–ester as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.19-4.16 (m, 2H), 2.67-2.64 (m, 2H), 2.60-2.57 (m, 2H), 0.99-0.96 (m, 2H), 0.02 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 178.4, 172.4, 63.2, 29.1, 17.4, –1.4.

Following a reported procedure[35] with modifications, the crude oil (assumed 1.00 mol) was dissolved in nitromethane (1800 mL) and cooled to 0 °C (ice-water bath). The solution was treated portion-wise with CDI (200 g, 1.23 mmol) in solid form for 30 min. The reaction mixture was allowed to warm overnight to room temperature. Then, the resulting mixture was cooled to 0 °C (ice-water bath) and slowly treated with *tert*-BuOK (168.32 g, 1.5000 mmol) over 30 min [Caution: adding base all-at-once can cause an explosion!]. The suspension was stirred at room temperature for 12 h before being quenched by the slow addition of a solution of aqueous HCl (1 M, 1 L). The mixture was allowed to stir for 15 min at room temperature. The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2 (500 mL x 3). The combined organic extract was dried over Na_2SO_4 and concentrated under vacuum to obtain the succinic ester–nitroketone as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.37 (s, 2H), 4.18-4.15 (m, 2H), 2.80-2.78 (m, 2H), 2.70-2.68 (m, 2H), 0.99-0.96 (m, 2H), 0.03 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 195.3, 172.2, 83.4, 63.6, 35.0, 28.3, 17.4, –1.4.

Following a reported procedure[35] with modifications, the crude oil was used for the next step without purification. The oil (assumed 1.00 mol) was dissolved in ACS-grade methanol (2 L) and cooled to 0 °C (ice-water bath). The solution was treated portion-wise with $NaBH_4$ (41.61 g, 1.100 mol) in solid form. The reaction mixture was stirred at 0 °C (ice-water bath) for 3 h. The resulting mixture was acidified by the addition of aqueous HCl (1 M) at 0 °C (ice-water bath) until the pH of the solution reached 1. The solution was concentrated under reduced pressure, and the remaining aqueous phase was extracted with CH_2Cl_2 (500 mL x 3). The combined organic extract was dried over Na_2SO_4 and concentrated under vacuum to obtain the succinic ester–nitroalcohol as an orange crude oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.45-4.35 (m, 3H), 4.20-4.15 (m, 2H), 2.53-2.49 (m, 2H), 1.88-1.78 (m, 2H), 1.00-0.96 (m, 2H), 0.04 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 173.8, 80.6, 68.0, 63.4, 30.3, 28.6, 17.4, –1.4.

Following a reported procedure[36] with modifications, the crude oil (assumed 1.0000 mol) was dissolved in anhydrous CH_2Cl_2 (1.25 L) and cooled to –10 °C (ice-acetone bath). Methanesulfonyl chloride (85.0 mL, 1.10 mol) was added all-at-once. The solution was treated dropwise with triethylamine (293.0 mL, 2.102 mol) over 15 min. The reaction mixture was stirred for 15 min at –10 °C (ice-acetone bath) and then quenched by the addition of aqueous HCl (1 M). The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2 (1 L x 3). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (5:1)] immediately (to avoid degradation) to obtain the title compound as a light-red oil (143.56 g, 58% for 4 steps). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.23 (m, 1H), 7.03-6.99 (m, 1H), 4.21-4.18 (m, 2H), 2.62-2.49 (m, 4H), 1.00-0.97 (m, 2H), 0.04 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 171.7, 140.50, 140.47, 63.4, 32.3, 23.8, 17.5, –1.4. HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{19}NO_4Si$: 246.1156, found: 246.1152.

2-(Trimethylsilyl)ethyl (*4S,5S*)-5-methyl-4-(nitromethyl)-6-oxohexanoate (2). Following a reported procedure,[45] a suspension of nitroalkene **1** (12.2683 g, 50.0033 mmol) in water (100 mL) was treated with (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (325.6 mg, 1.000 mmol, 2 mol%) and benzoic acid (1221.6 mg, 10.003 mmol). The suspension was cooled to 0 °C (ice-water bath). The reaction mixture was treated with propanal (7.50 mL, 104 mmol) in one portion. After 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and then stirred until nitroalkene **2** was consumed (the course of the reaction was monitored in 15 min intervals by TLC analysis on silica using hexanes/ethyl acetate (5:1)), which usually required 1.5 h. The reaction was then quenched by the addition of 1 M aqueous HCl (100 mL), and the resulting mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic extract was washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried over Na_2SO_4, and then concentrated to obtain a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.67 (s, 1H), 4.53-4.40 (m, 2H), 4.18-4.14 (m, 3H), 2.78-2.74 (m, 1H), 2.62-2.57 (m, 1H), 2.35 (t, J = 7.25 Hz, 2H), 1.78-1.57 (m, 2H), 1.17 (d, J = 7.4 Hz, 3H), 0.99-0.96 (m, 3H), 0.03 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 203.8, 174.0, 78.1, 64.6, 48.6, 38.2, 33.3, 25.2, 18.8, 10.7, 0.0. HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{25}NO_5Si$: 304.1575, found: 304.1570.

(*E*/*Z*)-1-Nitroprop-1-ene (3). Following a reported procedure[37] but at larger scale, a solution of acetaldehyde (44.05 g, 0.9999 mol) and nitromethane (122.10 g, 2.0003 mol) in 2-propanol (500 mL) at 0 °C (ice-water bath) under argon was treated with a catalytic amount of KF (5.80 g, 99.8 mmol). The resulting mixture was allowed to warm overnight to room temperature and then treated with water (150 mL). The latter mixture was extracted with diethyl ether (500 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain the nitroalcohol as a colorless oil (78.86 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53-4.48 (m, 1H), 4.42-4.34 (m, 2H), 2.75 (d, J = 4.5 Hz, 1H), 1.29 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 81.5, 65.0, 19.8. HRMS (ESI-FTMS) (*m/z*): $[M–H]^–$ calcd for $C_3H_6NO_3$: 104.03532, found: 104.03428.

Following a reported procedure[38] with modifications, a mixture of the crude nitroalcohol (26.27 g, assumed 250.0 mmol) and *o*-phthalic anhydride (48.25 g, 325.8 mmol) was placed in a 100-mL round-bottle flask fitted with a 10-cm vacuum-insulated Vigreux column, a water condenser, and a 50-mL round-bottomed collection flask (at –78 °C; dry ice-acetone bath). The reaction flask was heated from room temperature to 150 °C (oil bath temperature) and kept at 150 °C (oil bath temperature) for 4 h under reduced pressure (110 mmHg), then the oil bath temperature was raised to 160 °C and kept at the same temperature for 2 h. As the initially colorless reaction mixture darkened, the title compound was collected as a light-yellow distillate along with water (boiling point 35–40 °C via an overhead thermometer; 110 mmHg). The distillate was dried over Na_2SO_4 to obtain the title compound as a light-yellow oil (17.553 g, 81%), which was stored in the dark under argon at –20 °C until use. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dq, J = 12.5, 7.3 Hz, 1H), 7.02 (dq, J = 13.2, 1.7 Hz, 1H), 1.96 (dd, J = 7.4, 1.8 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.6, 138.2, 136.4, 14.0. HRMS (ESI-FTMS) (*m/z*): $[M–H]^–$ calcd for $C_3H_4NO_2$: 86.02475, found: 86.02367.

(2*R*,3*R*)-2-Ethyl-3-methyl-4-nitrobutanal (4). Following a reported procedure[45] with modifications, a suspension of nitroalkene **3** (5.66 g, 65.0 mmol) in water (130 mL) was treated with (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (423.2 mg, 1.328 mmol, 2 mol%) and benzoic acid (1588.1 mg, 13.004 mmol) at 0 °C (ice-water bath) and subsequently treated with butanal (11.7 mL, 130 mmol) in a dropwise manner. The reaction mixture was stirred until nitroalkene **2** was consumed (the course of the reaction was monitored by ^{1}H NMR analysis, typically 135 min) at 0 °C (ice-water bath). The reaction was then quenched by the addition of a 1 M aqueous HCl (150 mL), and the resulting mixture was extracted with CH_2Cl_2 (100 mL x 3). The combined organic extract was washed with a saturated aqueous solution of $NaHCO_3$ (150 mL), dried over Na_2SO_4, and then concentrated to obtain a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, J = 1.7 Hz, 1H), 4.44 (dd, J = 12.1, 5.6 Hz, 1H), 4.34 (dd, J = 12.1, 8.0 Hz, 1H), 2.78 (ddd, J = 13.6, 7.7, 6.2 Hz, 1H), 2.38 – 2.27 (m, 1H), 1.81 – 1.72 (m, 1H), 1.69 – 1.62 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 203.0, 79.1, 54.9, 31.2, 18.4, 14.6, 11.5.

3-((3*S*,4*S*)-4-Methyl-1-tosylpyrrolidin-3-yl)propanoic acid (5). Follow a reported procedure,[46] a solution of nitroaldehyde **2** (60.7 mg, 0.200 mmol) in AcOH/H_2O (1:1 v/v; 5 mL) was treated with Zn powder (327 mg, 5.00 mmol) in portion-wise manner at 0 °C (ice-water bath). The resulting mixture was allowed to warm to room temperature overnight, upon which the reaction mixture was filtered through a Celite pad and washed with H_2O (3 mL x 3) and CH_2Cl_2 (5 mL x 3). The combined filtrate was treated with 4 M aqueous NaOH solution until pH = 12 at 0 °C (ice-water bath). The organic layer was separated, and the aqueous layer was re-extracted with CH_2Cl_2 (5 mL x 3). The combined organic extract was dried over Na_2SO_4 and then concentrated under reduced pressure to obtain a colorless oil. The oil was dissolved in CH_2Cl_2 (2 mL) and treated with triethylamine (60 µL, 0.43 mmol) and *p*-toluenesulfonyl chloride (57.20 mg, 0.3 mmol) at 0 °C (ice-water bath). The resulting mixture was allowed to warm to room temperature overnight before quenching by the addition of saturated aqueous NH_4Cl solution (5 mL). The organic layer was separated, and the aqueous layer was re-extracted with CH_2Cl_2 (3 mL x 3). The combined organic extract was dried over Na_2SO_4 and then concentrated under reduced pressure, chromatographed [silica, hexanes/ethyl acetate (5:1)] to obtain 2-(trimethylsilyl)ethyl 3-((3*S*,4*S*)-4-methyl-1-tosylpyrrolidin-3-yl)propanoate (**5-R**) as an off-white solid (60.1 mg, 73%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 4.14 (td, J = 8.2, 1.5 Hz, 2H), 3.52 – 3.44 (m, 2H), 2.86 – 2.72 (m, 2H), 2.43 (s, 3H), 2.28 – 2.14 (m, 2H), 1.82 (dddd, J = 13.5, 9.0, 6.9, 4.4 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.56 (dtd, J = 13.1, 9.1, 6.0 Hz, 1H), 1.35 (dtd, J = 13.5, 9.3, 5.9 Hz, 1H), 0.98 – 0.95 (m, 2H), 0.93 (dd, J = 6.6, 1.2 Hz, 3H), 0.04 (s, 9H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 173.2, 143.5, 134.0, 129.8, 127.6, 62.9, 54.9, 53.2, 45.3, 39.0, 32.9, 27.1, 21.7, 17.5, 16.4, –1.4.

Follow a reported procedure,[47] a solution of the above sample of **5-R** (60.1 mg, 0.146 mmol) in CH_2Cl_2 (0.5 mL) was treated with TFA (0.5 mL) at 0 °C (ice-water bath). The resulting mixture was allowed to warm to room temperature overnight and then concentrated under reduced pressure, chromatographed [silica, hexanes/ethyl acetate (1% v/v acetic acid, 2:1)] to obtain an off-white solid (45.15 mg, 99%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 2H), 7.35 – 7.30

(m, 2H), 3.50 (ddd, J = 12.4, 9.8, 7.5 Hz, 2H), 2.84 (dd, J = 9.8, 8.6 Hz, 1H), 2.79 (dd, J = 9.8, 8.8 Hz, 1H)., 2.43 (s, 3H), 2.37 – 2.20 (m, 2H), 1.82 (dddd, J = 13.6, 9.1, 7.0, 4.3 Hz, 1H), 1.76 – 1.66 (m, 1H), 1.62 – 1.53 (m, 1H), 1.42 – 1.32 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 178.7, 143.6, 133.8, 129.8, 127.6, 54.8, 53.0, 45.1, 39.0, 32.4, 26.8, 21.6, 16.4. HRMS (ESI-FTMS) (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{22}NO_4S$ 312.12641; found 312.12632.

2-(Trimethylsilyl)ethyl (*4S,5S*)-5-methyl-4-(nitromethyl)hept-6-ynoate (6). Following a reported procedure[48,49] with modifications, a solution of *tert*-BuOK (11.25 g, 100.2 mmol) in distilled THF (450 mL) was cooled to –78 °C (dry ice – acetone bath) and treated with a solution of the Seyferth-Gilbert reagent (15.00 g, 99.95 mmol) in distilled THF (75 mL). The resulting mixture was stirred at –78 °C (dry ice-acetone bath) for 30 min, and then treated dropwise with a solution of above crude aldehyde **2** (assumed 50.0 mmol) in distilled THF (64 mL). The reaction mixture was stirred at –78 °C (dry ice-acetone bath) for 12 h, and then was allowed to warm to room temperature over 12 h. The reaction mixture was then treated with saturated aqueous NH_4Cl (500 mL) and extracted with CH_2Cl_2 (200 mL x 3). The combined organic extract was washed with water (500 mL) and brine (500 mL), dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (7:1)] to obtain a colorless oil (10.58 g, 71% from **1**) (estimated *dr* = 4.9:1 on the basis of the ^1H NMR integration of the propionate α-methylene protons). ^1H NMR ($CDCl_3$, 500 MHz) δ 4.58-4.53 (m, 1H), 4.40-4.36 (m, 1H), 4.18-4.14 (m, 2H), 2.74-2.68 (m, 1H), 2.43-2.28 (m, 3H), 2.12 (d, J = 2.55 Hz, 1H), 1.94-1.87 (m, 1H), 1.81-1.74 (m, 1H), 1.25 (d, J = 7.15 Hz, 3H), 0.99-0.96 (m, 2H), 0.03 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 127.7, 84.2, 76.9, 71.5, 63.1, 41.2, 31.6, 27.4, 25.9, 18.6, 17.4, –1.4. $[\alpha]_D^{21}$ = +13.3 ° (CH_2Cl_2, c 0.23) HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{25}NO_4Si$: 300.1626, found: 300.1620.

2-(Trimethylsilyl)ethyl (*4S,5S*)-4-(2-hydroxy-1-nitroethyl)-5-methylhept-6-ynoate (7). Following a reported procedure[50] with modifications, a solution of alkyne **6** (10.58 g, 35.33 mmol) in distilled THF (180 mL) was treated with paraformaldehyde (4.25 g, 128 mmol). The resulting suspension was cooled to 0 °C (ice-water bath) and treated with NaOAc (0.875 g, 10.7 mmol). After 30 min, the mixture was allowed to warm to 40 °C (water bath) and stirred for 2 days. The reaction mixture was filtered. The filter cake was washed with CH_2Cl_2 (30 mL x 3). The combined filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to obtain a colorless oil (5.45 g, 47%). ^1H NMR ($CDCl_3$, 500 MHz) δ 4.78-4.75 (m, 1H), 4.27-4.13 (m, 4H), 2.72 -2.68 (m, 1H), 2.47-2.31 (m, 4H), 2.18 (d, J = 2.6 Hz, 1H), 1.82-1.78 (m, 2H), 1.28 (d, J = 7.1 Hz, 3H), 0.99-0.96 (m, 2H), 0.04 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 172.9, 90.0, 84.8, 72.0, 63.2, 60.6, 43.1, 32.5, 27.1, 23.1, 18.2, 17.4, –1.4. HRMS (ESI-FTMS) (*m/z*): $[M–H]^–$ calcd for $C_{15}H_{27}NO_5Si$: 328.1586, found: 328.1586.

2-(Trimethylsilyl)ethyl (*4S,5S*)-5-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)acetyl)hept-6-ynoate (8). Following a reported procedure[54] with modifications, a solution of nitroalcohol **7** (3.29 g, 9.99 mmol) in anhydrous CH_2Cl_2 (70 mL) was cooled to 0 °C (ice-water bath), and treated with pyridinium *p*-toluenesulfonate (249.6 mg, 0.99343 mmol). The resulting

mixture was treated in a dropwise manner with 3,4-dihydropyran (1.40 mL, 15.3 mmol) for 15 min at 0 °C (ice-water bath) under argon atmosphere, and then allowed to warm overnight to room temperature. The reaction mixture was diluted with diethyl ether (430 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and used for the next step without further purification.

Following a reported procedure[53] with modifications, a solution of the above protected alcohol **5** (assumed 9.99 mmol) in anhydrous THF (100 mL) was cooled to 0 °C (ice-water bath) and treated dropwise over 15 min with a solution of *tert*-BuOK (1.2356 g, 11.011 mmol) in anhydrous THF (110 mL) under argon. The resulting mixture was stirred for 15 min at the same condition before cooled to –78 °C (dry ice-acetone bath), and added a solution of DMDO in acetone (170 mL, *ca.* 0.065 M). The reaction mixture was stirred for 20 min under argon and then quenched by the addition of a 0.1 M aqueous solution of phosphate buffer (150 mL, pH 7). The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2 (500 mL x 3). The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was filtered through a silica plug to eliminate the precipitant [silica, CH_2Cl_2/hexanes (1:1)]. The filtrate was concentrated to dryness under reduced pressure to afford a colorless oil (2.3494 g), which was used for the next step without any further purification. HRMS (ESI-FTMS) (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{34}O_5Si$: 405.2068, found: 405.2065.

2-(Trimethylsilyl)ethyl (*4S,5S*)-7-(4-acetyl-3-methyl-1*H*-pyrrol-2-yl)-5-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)acetyl)hept-6-ynoate (10). Following a reported procedure[55] with modifications, a solution of pre-D **8** (2.349 g, assumed 6.374 mmol), iodopyrrole pre-A **9** (1.7464 g, 7.0123 mmol), and triethylamine (2.95 mL, 21.2 mmol) in anhydrous DMF (20 mL) was subjected to four freeze-pump-thaw cycles. The reaction mixture was then treated with $Pd(PPh_3)_4$ (810.3 mg, 0.7012 mmol) and CuI (293.8 mg, 1.543 mmol) under argon, and stirred for 24 h at room temperature. The resulting mixture was quenched by the addition of water (100 mL), and the suspension was extracted with ethyl acetate (30 mL x 3). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, ethyl acetate/CH_2Cl_2 (5:95)] to obtain a brown oil (1.6907 g total, 33% from **7**) as 2 fractions, which were attributed to diastereomers given the undefined stereocenter of the THP protecting group. The two fractions were analyzed separately, then combined for use in subsequent reactions. HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{42}NO_6Si$: 504.27759, found: 504.27664.

1st fraction (1.2386 g, 38%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 10.06 (br s, 1H), 7.21 (d, J = 3.3 Hz, 1H), 4.96 – 4.95 (m, 1H), 4.71 (d, J = 18.7 Hz, 1H), 4.30 (d, J = 18.9 Hz, 1H), 4.16 – 4.14 (m, 2H), 3.91 – 3.88 (m, 1H), 3.63 – 3.60 (m, 1H), 2.84 – 2.80 (m, 1H), 2.63 – 2.60 (m, 1H), 2.37 (s, 3H), 2.34 – 2.29 (m, 4H), 2.20 – 2.15 (m, 1H), 1.97 – 1.85 (m, 4H), 1.78 – 1.69 (m, 2H), 1.62 – 1.59 (m, 2H), 1.33 (d, J = 6.9 Hz, 3H), 0.98 – 0.96 (m, 2H), 0.04 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz) δ 210.4, 193.9, 172.9, 125.9, 125.1, 124.2, 113.6, 96.6, 95.5, 74.3, 72.8, 63.1, 61.2, 51.5, 32.1, 29.9, 29.5, 28.0, 25.6, 24.6, 19.2, 17.8, 17.5, 11.9, –1.4.

2nd fraction (0.4521 g, 14%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 9.67 (br s, 1H), 7.23 (d, J = 3.3 Hz, 1H), 4.76 – 4.75 (m, 1H), 4.60 (d, J = 18.2 Hz, 1H), 4.35 (d, J = 18.2 Hz, 1H), 4.16 – 4.14 (m, 2H), 4.00 – 3.97 (m, 1H), 3.53 – 3.50 (m, 1H), 2.90 – 2.86 (m, 1H), 2.69 – 2.66 (m, 1H), 2.37

(s, 3H), 2.34 – 2.30 (m, 4H), 2.23 – 2.18 (m, 1H), 1.99 – 1.95 (m, 2H), 1.92 – 1.88 (m, 1H), 1.81 – 1.76 (m, 3H), 1.64 – 1.58 (m, 2H), 1.30 (d, J = 6.9 Hz, 3H), 0.98 – 0.95 (m, 2H), 0.03 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz) δ 210.6, 195.3, 174.4, 126.9, 126.5, 125.6, 115.1, 100.4, 97.1, 75.6, 75.3, 64.4, 63.8, 53.9, 33.5, 31.7, 30.5, 29.4, 26.8, 25.7, 20.4, 20.1, 18.9, 13.3, 0.0.

2-(Trimethylsilyl)ethyl (*4S,5S*)-7-(4-acetyl-3-methyl-1*H*-pyrrol-2-yl)-4-(2-hydroxyacetyl)-5-methyl-6-oxoheptanoate (11). Following a reported procedure[58] with modifications, a solution of alkynylpyrrole **10** (combined fractions from above, 6.0418 g, 11.995 mmol) in anhydrous acetonitrile:water (44 mL total, 25:1) was subjected to four freeze-pump-thaw cycles. The reaction mixture was then treated with $PdCl_2(MeCN)_2$ (155.6 mg, 0.5997 mmol, 5 mol%) under argon and stirred at room temperature for 24 h. The resulting mixture was diluted with ethyl acetate (200 mL) and washed with brine (100 mL). The organic layer was collected, and the aqueous layer was reextracted with ethyl acetate (50 mL x 3). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, ethyl acetate/hexanes (2:1)] to obtain a brown paste (2.30 g, 44%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 9.27 (br s, 1H), 7.29 (d, J = 3.2 Hz, 1H), 4.34 (s, 2H), 4.14 – 4.12 (m, 2H), 3.77 – 3.63 (m, 2H), 3.05 – 3.01 (m, 1H), 2.93 – 2.89 (m, 1H), 2.35 (s, 3H), 2.24 – 2.21 (m, 4H), 2.14 – 2.11 (m, 1H), 1.95 – 1.91 (m, 1H), 1.88 – 1.84 (m, 1H), 1.14 (d, J = 7.3 Hz, 3H), 0.96 – 0.93 (m, 2H), 0.02 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz) δ 213.6, 211.12, 194.7, 172.7, 124.8, 124.2, 122.5, 117.6, 68.8, 63.3, 48.0, 46.6, 37.5, 30.7, 27.8, 23.6, 17.4, 14.2, 10.8, – 1.4. $[\alpha]_D^{22}$ = –4.4 ° (CH_2Cl_2, c 0.83) HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{35}NO_6Si$: 438.2306, found: 438.2298.

(*2S,3S*)-8-Acetyl-2-(3-(2-(trimethylsilyl)ethyl)oxy-3-oxopropan-1-yl)-2,3-dihydro-1-hydroxymethyl-3,7-dimethyldipyrrin (12). Following a reported procedure[60] with modifications, a solution of mixture of 1,4-diketone **11** (1.1422 g, 2.6101 mmol) in anhydrous DMF (30 mL) was treated with ammonium acetate (2.0119 g, 26.101 mmol, 10 equiv) under argon. The reaction mixture was stirred at room temperature, and monitored by absorption spectroscopy (growth in absorption at ~325 nm). After 30 min, the reaction mixture was cooled in an ice-water bath, diluted with cooled ethyl acetate (5 mL, pre-cooled in ice-water bath) and washed with cooled saturated aqueous solution of KH_2PO_4 (5 mL, pre-cooled in ice-water bath). The organic layer was collected and the aqueous layer was reextracted with ethyl acetate (5 mL x 2). The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed [deactivated silica, pre-treated with 1% triethylamine in hexanes (v/v); ethyl acetate/hexanes/triethylamine (50:50:1)] to obtain a brown paste (642.9 mg, 59%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.72 (brs, 1H), 7.37 (d, J = 3.2 Hz, 1H), 5.90 (s, 1H), 4.68 – 4.41 (m, 2H), 4.21 – 4.08 (m, 2H), 2.75 – 2.66 (m, 1H), 2.64 – 2.53 (m, 1H), 2.45 – 2.32 (m, 8H), 2.10 – 2.02 (m, 1H), 1.72 – 1.64 (m, 1H), 1.23 (d, J = 7.1 Hz, 3H), 1.03 – 0.90 (m, 2H), 0.04 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz) δ 194.6, 182.3, 173.1, 154.9, 129.2, 125.8, 124.4, 118.7, 104.6, 63.2, 61.9, 54.2, 41.9, 31.7, 27.9, 26.9, 21.3, 17.5, 10.8, – 1.4. HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{34}N_2O_4Si$: 419.2361, found: 419.2352.

(*2S,3S*)-8-Acetyl-2-(3-(2-(trimethylsilyl)ethyl)oxy-3-oxopropan-1-yl)-2,3-dihydro-1-formyl-3,7-dimethyldipyrrin (13). *Large-scale preparation from **12**:* Following a reported procedure[61,62] with modifications, a solution of 1-hydroxymethyldihydrodipyrrin **12** (642.9 mg, 1.536 mmol) in anhydrous DMSO (9.2 mL) was added a solution of IBX (437.1 mg, 1.689 mmol, 1.1 equiv) in anhydrous DMSO (6.2 mL) under argon. The reaction mixture was stirred at room temperature and monitored by absorption spectroscopy (growth in absorption at ~435 nm). After 20 min, the reaction mixture was diluted with diethyl ether (150 mL, pre-cooled in an ice-water bath) and washed with 0.1 M aqueous solution of phosphate buffer (100 mL, pH 7, pre-cooled in an ice-water bath). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [deactivated silica, pre-treated with 1% triethylamine in hexanes (v/v); ethyl acetate/hexanes/triethylamine (50:50:1)] to obtain a brown-red paste (101.4 mg, 16%).

*Small-scale preparation from **12**:* In a similar manner, a solution of 1-hydroxymethyldihydrodipyrrin **12** (91.0 mg, 0.217 mmol) in anhydrous DMSO (1.3 mL) was treated with a solution of IBX (73.0 mg, 0.261 mmol) in anhydrous DMSO (0.586 mL) under argon. The reaction mixture was stirred at room temperature and monitored by absorption spectroscopy (growth in absorption at ~435 nm). After 20 min, the reaction mixture was diluted with diethyl ether (10 mL, pre-cooled in ice-water bath) and filtered through a short pad of Celite. The filter cake was washed with diethyl ether (5 mL x 3). The combined filtrate was washed with a 0.1 M aqueous solution of phosphate buffer (10 mL, pH 7, pre-cooled in an ice-water bath). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [deactivated silica, pre-treated with 1% triethylamine in hexanes (v/v); ethyl acetate/hexanes/triethylamine (50:50:1)] to obtain a brown-red paste (30.5 mg, 34%).

^{1}H NMR ($CDCl_3$, 700 MHz) δ 10.76 (br s, 1H), 9.93 (s, 1H), 7.46 (d, J = 3.3 Hz, 1H), 6.26 (s, 1H), 4.13 – 4.11 (m, 2H), 2.83 – 2.81 (m, 1H), 2.74 – 2.71 (m, 1H), 2.38 (s, 3H), 2.37 (s, 3H), 2.30 – 2.28 (m, 2H), 2.15 – 2.10 (m, 1H), 1.72 – 1.67 (m, 1H), 1.19 (d, J = 7.2 Hz, 3H), 0.95 – 0.92 (m, 2H), 0.00 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz) δ 194.3, 189.9, 173.0, 172.7, 156.1, 129.5, 127.8, 124.9, 123.4, 113.3, 63.0, 51.7, 42.2, 32.0, 28.1, 27.1, 21.8, 17.5, 11.0, –1.4. HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{32}N_2O_4Si$: 417.2204, found: 417.2197.

*Streamlined preparation from **11**:* A solution of 1,4-diketone **11** (452.7 mg, 1.034 mmol) in anhydrous DMSO (12 mL) under argon was treated with ammonium acetate (797.4 mg, 10.34 mmol, 10 equiv). The reaction mixture was stirred at room temperature and monitored by absorption spectroscopy. After 30 min, the reaction mixture was cooled in an ice-water bath, diluted with ethyl acetate (5 mL, pre-cooled in an ice-water bath) and washed with saturated aqueous KH_2PO_4 (5 mL, pre-cooled in an ice-water bath). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (5 mL x 2). The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was dissolved in anhydrous DMSO (6.2 mL) under argon and treated with a solution of IBX (348.0 mg, 1.344 mmol, 1.3 equiv) in anhydrous DMSO (2.8 mL). The reaction mixture was stirred at room temperature and monitored by absorption spectroscopy (whereupon a growth in absorption at ~435 nm was observed). After 20 min, the reaction mixture was diluted with diethyl ether (150 mL, pre-cooled in an ice-water bath) and then filtered through a short pad of Celite. The filter

cake was washed with diethyl ether (10 mL x 3). The combined filtrate was washed with a 0.1 M aqueous solution of phosphate buffer (KH_2PO_4 and K_2HPO_4, pH 7, 50 mL, pre-cooled in an ice-water bath). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [deactivated silica, pre-treated with 1% triethylamine in hexanes (v/v); ethyl acetate/hexanes/triethylamine (50:50:1)] to obtain a brown-red paste (95.63 mg, 22% overall in 2 steps). The characterization data (^{1}H NMR and $^{13}C\{^1H\}$ NMR analysis) were identical as above. $[\alpha]_D^{21}$ = –15.9 ° (CH_2Cl_2, c 0.19) HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{32}N_2O_4Si$: 417.2204, found: 417.2189.

(3*R*,4*R*)-3-Ethyl-4-methyl-5-nitropent-1-yne (14). Following a reported procedure[48,49] with modifications, a solution of *tert*-BuOK (14.62 g, 130.3 mmol) in freshly distilled THF (580 mL) was cooled to –78 °C (dry ice-acetone bath) and treated with a solution of dimethyl (diazomethyl)phosphonate (Seyferth-Gilbert reagent, 19.50 g, 129.9 mmol) in distilled THF (100 mL). The resulting mixture was stirred at –78 °C (dry ice-acetone bath) for 30 min, and then treated dropwise with a solution of crude aldehyde **4** (assumed 65.0 mmol) in distilled THF (80 mL). The reaction mixture was stirred at –78 °C (dry ice-acetone bath) for 12 h, and then was allowed to warm to room temperature over 12 h. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (750 mL). The resulting mixture was extracted with CH_2Cl_2 (250 mL x 3). The combined organic extract was washed with water (500 mL) and brine (500 mL). The resulting mixture was dried over Na_2SO_4, concentrated under reduced pressure (≥ 100 mbar), and chromatographed [silica, short-pad, hexanes/ethyl acetate (20:1)] to obtain a yellowish oil (7.34 g, 73% from **3**). (*dr* = 23:1 on the basis of the ^{1}H NMR integration of the alkynyl proton resonance). Note: the title compound is volatile under high-vacuum at room temperature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.30 (dd, *J* = 12.1, 9.5 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.33 – 2.29 (m, 1H), 2.16 (d, *J* = 2.5 Hz, 1H), 1.63 – 1.56 (m, 1H), 1.52 – 1.43 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 1.06 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 83.7, 79.4, 77.4, 77.2, 76.9, 72.2, 37.5, 35.8, 25.6, 16.5, 11.9. $[\alpha]_D^{18}$ = +2.1 ° (CH_2Cl_2, c 1.15). HRMS (ESI-FTMS) (*m/z*): $[M–H]^-$ calcd for $C_8H_{12}NO_2$: 154.08735, found: 154.08666.

(2*R*,3*R*)-3-Ethyl-2-methylpent-4-ynoic acid (15). Following a reported procedure,[64] a solution of 5-nitropentyne **14** (7.34 g, 47.3 mmol) and acetic acid (27.0 mL, 472 mmol) in anhydrous DMSO (94 mL) was heated to 35 °C (oil bath temperature) and treated with $NaNO_2$ (9790.5 mg, 141.90 mmol) in one batch under argon. The solution was stirred at the same condition for 6 h followed by the addition of 2 M HCl solution (200 mL) (Caution: possible production of poisonous NO_2 gas!). The resulting mixture was extracted with ethyl acetate (75 mL x 4). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (1% v/v acetic acid, 2:1)] to obtain a yellowish oil (6.31 g, 95%) (*dr* = 33:1 on the basis of the ^{1}H NMR integration of the alkynyl proton resonance). ^{1}H NMR (700 MHz, $CDCl_3$) δ 2.71 – 2.63 (m, 2H), 2.13 (d, *J* = 2.4 Hz, 1H), 1.59 – 1.47 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 180.4, 84.9, 77.3, 77.2, 77.0, 71.0, 43.2, 36.1, 24.2, 13.8, 12.0. $[\alpha]_D^{24}$ = –7.15 ° (CH_2Cl_2, c 1.01). HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_8H_{13}O_2$: 141.09100, found: 141.09105.

Derivatives **16a** and **16b**: A solution of pentynoic acid **15** (140.18 mg, 1.0000 mmol) in CH_2Cl_2 (5 mL) at 0 °C (ice-water bath) was treated with EDC (233.00 mg, 1.5009 mmol), triethylamine (0.25 mL, 1.8 mmol), and DMAP (24.4 mg, 0.20 mmol) followed by 3,5-dibromoaniline (381.4 mg, 1.520 mmol) or 3,5-dimethylaniline (184.2 mg, 1.52 mmol). The resulting mixture was allowed to warm to room temperature over 12 h before quenching by the addition of 2 M aqueous HCl solution (10 mL). The organic layer was separated, and the aqueous layer was re-extracted with CH_2Cl_2 (5 mL x 3). The combined organic extract was dried over Na_2SO_4 and then concentrated under reduced pressure followed by chromatography [silica, hexanes/ethyl acetate (5:1)] to obtain an off-white solid.

(2*R*,3*R*)-*N*-(3,5-Dibromophenyl)-3-ethyl-2-methylpent-4-ynamide (16a). (283.55 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.69 (d, J = 1.7 Hz, 2H), 7.39 (t, J = 1.7 Hz, 1H), 2.62 – 2.48 (m, 2H), 2.32 (d, J = 2.2 Hz, 1H), 1.70 – 1.60 (m, 1H), 1.55 – 1.45 (m, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.06 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.0, 140.1, 129.8, 123.1, 121.5, 85.1, 72.9, 36.9, 25.4, 16.1, 11.8. $[\alpha]_D^{22}$ = +5.8 ° (CH_2Cl_2, c 0.66). HRMS (ESI-FTMS) (*m/z*) $[M+H]^+$ calcd for $C_{14}H_{16}Br_2NO$ 371.95932; found 371.95961.

(2*R*,3*R*)-*N*-(3,5-Dimethylphenyl)-3-ethyl-2-methylpent-4-ynamide (16b). (199.55 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.17 (s, 2H), 6.75 (s, 1H), 2.59 (dddd, J = 9.5, 7.0, 4.7, 2.5 Hz, 1H), 2.53 (p, J = 6.9 Hz, 1H), 2.31 – 2.26 (m, 7H), 1.74 – 1.62 (m, 1H), 1.60 – 1.45 (m, 1H), 1.33 (d, J = 7.0 Hz, 3H), 1.06 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.7, 138.8, 137.9, 126.1, 117.8, 85.3, 72.4, 46.0, 37.0, 25.2, 21.5, 16.0, 11.8. $[\alpha]_D^{21}$ = –11.6 ° (CH_2Cl_2, c 0.58). HRMS (ESI-FTMS) (*m/z*) $[M+H]^+$ calcd for $C_{16}H_{22}NO$ 244.16959; found 244.16966.

(2*R*,3*R*)-1-(1,3-Dithian-2-yl)-3-ethyl-2-methylpent-4-yn-1-ol (17). A solution of the viscous oil **15** (5.61 g, 40.0 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C (ice-water bath) under argon was treated with 1,1′-carbonyldiimidazole (8.4354 g, 52.022 mmol) in one portion. The reaction mixture was stirred for 3 h, and then treated with (MeO)NHMe·HCl (9.7581 g, 100.04 mmol). The resulting mixture was allowed to warm to room temperature over 12 h before quenching by the addition of 2 M aqueous HCl solution (150 mL). The organic layer was separated, and the aqueous layer was re-extracted with CH_2Cl_2 (75 mL x 3). The combined organic extract was dried over Na_2SO_4 and then concentrated under reduced pressure to obtain a crude viscous oil, which was used for the next reaction without any further purification. A solution of 1,3-dithiane (16.00 g, 133.1 mmol) in freshly distilled THF (665 mL) at –78 °C under argon was treated dropwise with *n*-BuLi (53.0 mL, 130 mmol, 2.5 M in hexanes) for 15 min. The reaction mixture was allowed to warm to –20 °C (dry ice-brine bath) and stirred for 1 h under argon. The solution, now containing lithiated dithiane, was treated at –78 °C with a solution of above crude oil (assumed 40.0 mmol) in anhydrous THF (80 mL). The resulting mixture was stirred overnight at –78 °C and then treated with glacial acetic acid (8.0 mL, 140 mmol), anhydrous methanol (200 mL), and one portion of $NaBH_4$ (6.05 g, 160 mmol). The mixture was then placed in an ice-water bath at 0 °C and stirred for 3 h before the addition of a saturated aqueous solution of NH_4Cl (700 mL). The mixture was extracted with CH_2Cl_2 (500 mL x 3). The combined organic extract was dried over

Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (7:1)] to obtain a semi-solid product that solidified upon storage at –20 °C (6.7635 g, 69%). Mp 55-56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (d, J = 3.8 Hz, 1H), 3.81 (dt, J = 8.5, 4.3 Hz, 1H), 3.04 – 2.85 (m, 3H), 2.80 (ddd, J = 13.8, 10.7, 2.7 Hz, 1H), 2.69 (dtd, J = 10.9, 4.2, 2.5 Hz, 1H), 2.34 (d, J = 4.9 Hz, 1H), 2.19 – 2.13 (m, 1H), 2.08 (dd, J = 7.9, 2.7 Hz, 2H), 1.97 – 1.88 (m, 1H), 1.55 (dtd, J = 11.4, 7.4, 3.7 Hz, 1H), 1.44 – 1.33 (m, 1H), 1.06 – 0.99 (m, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 87.4, 75.6, 70.4, 51.6, 39.6, 35.3, 29.9, 28.9, 25.9, 23.0, 13.5, 12.4. $[\alpha]_D^{24}$ = –3.3 ° (CH_2Cl_2, c 1.28). HRMS (ESI-FTMS) (*m/z*): [M–H]$^-$ calcd for $C_{12}H_{19}OS_2$: 243.08828, found: 243.08828.

(3*R*,4*R*)-4-Ethyl-1,1-dimethoxy-3-methylhex-5-yn-2-ol (18). Following a reported procedure[65] with modifications, a solution of alcohol **17** (4.9720 g, 20.343 mmol) in anhydrous methanol (200 mL) at 0 °C under argon was treated with bis(trifluoroacetoxy)iodobenzene (PIFA; 17.50 g, 40.69 mmol). The solution was stirred at 0 °C (ice-water bath) for 15 min, and then at room temperature for 150 min. The resulting mixture was treated with a 5% aqueous solution of $NaHCO_3$ (150 mL) and a saturated solution of $Na_2S_2O_3$ (150 mL). The resulting solution was extracted with diethyl ether (200 mL x 4). The combined organic extract was washed with a saturated aqueous solution of $NaHCO_3$ (100 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (100 mL) dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to obtain a colorless oil (3.12 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 4.3 Hz, 1H), 3.68 – 363 (m, 1H), 3.46 (s, 3H), 3.44 (s, 3H), 2.68 – 2.60 (m, 1H), 2.29 (d, J = 3.8 Hz, 1H), 2.07 (d, J = 2.5 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.60 – 1.53 (m, 1H), 1.42 – 1.32 (m, 1H), 1.03 (t, J = 7.4 Hz, 4H), 0.99 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 104.9, 87.6, 72.9, 70.0, 55.3, 55.2, 39.0, 35.1, 22.9, 12.8, 12.3. $[\alpha]_D^{24}$ = +10.9 ° (CH_2Cl_2, c 1.23). HRMS (ESI-FTMS) (*m/z*): [M+H]$^+$ calcd for $C_{11}H_{21}O_3$: 201.14852, found: 201.14856.

(3*R*,4*R*)-4-Ethyl-1,1-dimethoxy-3-methylhex-5-yn-2-one (19).[30] Following a reported procedure,[30] a solution of **18** (3.89 g, 19.4 mmol) in anhydrous CH_2Cl_2 (195 mL) at 0 °C (ice-water bath) under argon was treated with excess $NaHCO_3$ (16.3 g, 194 mmol) followed by a portion of Dess-Martin periodinane (DMP) (24.7 g, 58.3 mmol). [Note: in the absence of $NaHCO_3$, full epimerization of the configuration of the 3-methyl group was observed.] The resulting mixture was allowed to warm overnight to room temperature. The reaction mixture was then treated with a saturated aqueous solution of $NaHCO_3$ (100 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (100 mL). The biphasic solution was stirred for 20 min. The organic layer was separated and the aqueous layer was re-extracted with CH_2Cl_2 (150 mL x 3). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to obtain a colorless oil (3.83 g, quant.) (*dr* = 17:1 on the basis of the ^{1}H NMR integration of the alkynyl proton resonance). Characterization data (^{1}H NMR, ^{13}C{^{1}H} NMR, HRMS (ESI-FTMS)) agreed with the previous data.[30] ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.62 (s, 1H), 3.42 – 3.40 (m, 6H), 3.14 – 3.08 (m, 1H), 2.65 – 2.59 (m, 1 H), 2.06 (d, J = 2.4 Hz, 1H), 1.59 – 1.51 (m, 1H), 1.41– 1.33 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR

(175 MHz, $CDCl_3$) δ 207.0, 103.9, 85.9, 70.5, 55.0, 54.6, 44.8, 35.0, 23.8, 13.8, 11.5. HRMS (ESI-FTMS) (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{19}O_3$: 199.13287, found: 199.13292.

(2*R*,3*R*)-1-(1,1-Dimethoxymethyl)-8-(3-methoxy-1,3-dioxopropyl)-2,7-dimethyl-3-ethyl-2,3-dihydrodipyrrin (22).[30] Following a reported procedure[30,55] with modifications, a solution of pre-B **19** (3.63 g, 18.3 mmol), iodopyrrole pre-C **20** (5.63 g, 18.3 mmol) and triethylamine (7.65 mL, 55.0 mmol) in anhydrous DMF (65.4 mL) was subjected to four freeze-pump-thaw cycles. The reaction mixture was then treated with $Pd(PPh_3)_4$ (2115.78 mg, 1.83099 mmol) and CuI (697.41 mg, 3.6620 mmol) under argon, and stirred for 24 h at room temperature. The resulting mixture was quenched by the addition of water (500 mL), and the resulting suspension was extracted with ethyl acetate (200 mL x 3). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, ethyl acetate/hexanes (1:1)] to obtain known methyl 3-(5-((3*R*,4*R*)-3-ethyl-6,6-dimethoxy-4-methyl-5-oxohex-1-yn-1-yl)-4-methyl-1*H*-pyrrol-3-yl)-3-oxopropanoate (**21**)[30] a brown oil (5.03 g, 73%). HRMS (ESI-FTMS) (*m/z*): $[M-H]^-$ calcd for $C_{20}H_{26}O_6N$: 376.17656, found: 376.17675. Following a reported procedure[58] with modifications, a solution of **21** (4.84 g, 12.8 mmol) in anhydrous acetonitrile:water (23 mL total, 20:1) was subjected to four freeze-pump-thaw cycles. The reaction mixture was then treated with $PdCl_2(MeCN)_2$ (332.69 mg, 1.2822 mmol, 10 mol%) under argon and stirred at room temperature for 24 h. The resulting mixture was diluted with ethyl acetate (200 mL) and washed with brine (100 mL). The organic layer was collected and the aqueous layer was reextracted with ethyl acetate (50 mL x 3). The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was passed through a short silica pad using a mixture of ethyl acetate: hexanes (2:1) as eluent. The fraction containing the desired product was collected (3.38 g, assumed 8.54 mmol) and used for the next step[60] which entailed dissolution in anhydrous DMF (9 mL) followed by treatment with ammonium acetate (6.35 g, 82.4 mmol) under argon. After 120 min, the reaction mixture was cooled in an ice-water bath, diluted with ethyl acetate (100 mL, pre-cooled in ice-water bath) and washed with a saturated aqueous solution of KH_2PO_4 (250 mL, pre-cooled in ice-water bath). The organic layer was collected, and the aqueous layer was re-extracted with ethyl acetate (100 mL x 2). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [deactivated silica, pre-treated with 1% triethylamine in hexanes (v/v); ethyl acetate/hexanes/triethylamine (50:50:1)] to obtain a brown paste (1.22 g, 25% over 2 steps). The characterization data (^1H NMR and $^{13}C\{^1H\}$ NMR analysis) were identical with reported data.[30] ^1H NMR (700 MHz, $CDCl_3$) δ 11.15 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 5.96 (d, J = 1.6 Hz, 1H), 5.07 (s, 1H), 3.77 (s, 2H), 3.73 (s, 3H), 3.45 (s, 3H), 3.43 (s, 3H), 2.81 – 2.76 (m, 1H), 2.46 – 2.42 (m, 1H), 2.34 (s, 3H), 1.67 – 1.60 (m, 1H), 1.49 – 1.41 (m, 1H), 1.22 (d, J = 7.3 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 187.6, 180.1, 168.9, 154.8, 130.0, 126.3, 123.3, 119.3, 106.3, 102.3, 54.6, 54.5, 52.4, 51.0, 47.5, 46.9, 28.2, 18.6, 10.8, 10.7. $[\alpha]_D^{21}$ = –10.7 ° (CH_2Cl_2, c 0.31) HRMS (ESI-FTMS) (*m/z*): $[M-H]^-$ calcd for $C_{20}H_{27}O_5N_2$: 375.19255, found: 375.19273. The values of the molar absorption coefficient in acetonitrile at room temperature were determined to be: ε = 15,200 M^{-1} cm^{-1} at λ = 242 nm, ε = 11,300 M^{-1} cm^{-1} at λ = 331 nm.

3-[(*2S,3S*)-8-Acetyl-2-(3-(2-(trimethylsilyl)ethyl)oxy-3-oxopropan-1-yl)-2,3-dihydro-3,7-dimethyldipyrrin-1-yl]-1-[(*2R,3R*)-1-(1,1-dimethoxymethyl)-8-(3-methoxy-1,3-dioxopropyl)-2,7-dimethyl-3-ethyl-2,3-dihydrodipyrrin-8-yl]-2-(methoxycarbonyl)prop-2-en-1-one (23). *Early conditions:* Samples of **13** (62.49 mg, 150 μmol) and **22** (56.47 mg, 150 μmol) were treated with a solution of piperidine/acetic acid (15 mM/15 mM in acetonitrile, 3.75 mL) followed by addition of powdered 3 Å molecular sieves (60.3 mg). The reaction mixture was stirred at room temperature for 4 days, upon which the resulting mixture was filtered through a Celite pad and washed with CH_2Cl_2. The combined filtrate was concentrated and chromatographed [silica, diethyl ether/hexanes (3:2) then hexanes/ethyl acetate (1:1)] to afford two orange fractions. The first fraction (0.6 mg) consisted of the *Z*-isomer and a Mannich intermediate (in 1:1 ratio determined by RP-HPLC-MS analysis). The second fraction was the *E*-isomer of the title compound (13.1 mg, 11%): ^{1}H NMR (700 MHz, $CDCl_3$): δ 11.18 (brs, 1H), 10.28 (brs, 1H), 7.40 (s, 1H), 7.26 (s, 1H, overlapped with the solvent peak), 7.24 (brs, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.03 (s, 1H), 4.17–4.19 (m, 2H), 3.78 (s, 3H), 3.41 (s, 3H), 3.49 (s, 3H), 2.78 (qd, J = 7.4 and 2.9 Hz, 1H), 2.57–2.59 (m, 2H), 2.41–2.43 (m, 1H), 2.40 (s, 3H), 2.30–2.36 (m, 5H), 2.29 (s, 3H), 2.12 (dddd, J = 16.8, 9.0, 8.0, 3.3 Hz, 1H), 1.60–1.66 (m, 2H), 1.40–1.46(m, 1H), 1.20 (d, J = 7.3 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.98–1.00 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ -1.4, 10.78, 10.82, 10.9, 17.5, 18.6, 21.5, 27.6, 27.8, 28.3, 31.7, 41.4, 46.9, 51.0, 53.0, 54.5, 54.6, 56.0, 63.1, 102.2, 103.0, 105.9, 108.4, 118.6, 120.7, 123.2, 124.1, 127.7, 127.9, 129.5, 130.6, 131.0, 155.5, 156.2, 165.2, 171.1, 173.0, 180.7, 189.1, 194.3. HRMS (ESI-FTMS) (*m/z*) $[M+H]^+$ calcd for $C_{42}H_{59}N_4O_8Si$ 775.4097; found, 775.4092.

Refined conditions with improved catalysis: A solution of **13** (126.88 mg, 0.31611 mmol) and **22** (125.08 mg, 0.34772 mmol) in CH_2Cl_2 (3.2 mL) was treated with pyrrolidinium acetate (0.6 mL) and $Mg(OTf)_2$ (120.15 mg, 0.37263 mmol). The solution (containing ~85 mM reactants) was stirred at room temperature for 48 h and then diluted with CH_2Cl_2 (10 mL). The solution was washed with a 0.1 M aqueous solution of phosphate buffer (KH_2PO_4 and K_2HPO_4, pH 7, 100 mL). The organic layer was collected, and the aqueous layer was re-extracted with ethyl acetate (20 mL x 2). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [silica, diethyl ether/hexanes (1:1) then hexanes/ethyl acetate (1:1)] to afford an orange paste (85.1 mg, 35%). The characterization data (^{1}H NMR, ^{13}C{^{1}H} NMR) were identical as above. $[\alpha]_D^{20}$ = –17.1 ° (CH_2Cl_2, c 0.15). HRMS (ESI-FTMS) (*m/z*) $[M+H]^+$ calcd for $C_{42}H_{59}N_4O_8Si$ 775.40967; found 775.41006. The values of the molar absorption coefficient in acetonitrile at room temperature were determined to be: ε = 30,500 M^{-1} cm^{-1} at λ = 240 nm, ε = 16,100 M^{-1} cm^{-1} at λ = 332 nm, ε = 6,330 M^{-1} cm^{-1} at λ = 461 nm.

2-(Trimethylsilyl)ethyl bacteriopheophorbide *a* (24). *Early conditions:* A sample of **23** (13.1 mg, 16.9 μmol) in degassed acetonitrile (84.5 mL, 0.2 mM) was treated with $Yb(OTf)_3$ (105 mg, 169 μmol). The resulting solution was stirred under argon at 80 °C (oil bath) for 1 h. The mixture was concentrated to dryness under reduced pressure and then chromatographed [silica, CH_2Cl_2/ethyl acetate (25:1)] to afford a dark brown residue (5.56 mg). The sample through ^{1}H NMR and RP-HPLC analyses was found to consist of three components, namely, the title

compound and two products of allomerization: the 13^2-hydroxy derivative of the title compound, and the chlorin derivative thereof. The following data are only listed for the main epimer of the title compound: ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 6.09 (s, 1H), 4.26–4.31 (m, 2H), 3.98–4.08 (m, 4H), 3.85 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 3.16 (s, 3H), 2.50–2.56 (m, 1H), 2.41–2.46 (m, 1H), 2.32–2.38 (m, 1H), 2.26–2.31 (m, 1H), 2.17–2.21 (m, 1H), 2.04–2.11 (m, 1H), 1.79 (d, J = 7.4 Hz, 3H), 1.72 (d, J = 7.5 Hz, 3H), 1.11 (t, J = 7.3 Hz, 3H), 0.81–0.83 (m, 2H), 0.46 (br s, 1H), –0.05 (s, 9H), –0.97 (br s, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 199.3, 189.2, 173.2, 171.2, 169.74, 169.70, 163.8, 158.1, 148.2, 139.2, 138.4, 136.7, 136.4, 133.4, 128.8, 121.5, 108.2, 99.8, 97.8, 95.9, 64.5, 62.9, 55.1, 52.9, 50.8, 49.9, 49.0, 33.5, 30.3, 30.0, 29.8, 23.1, 23.0, 17.4, 13.4, 11.7, 10.9, –1.45; HRMS (ESI-FTMS) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{51}N_4O_6Si$ 711.3572; found 711.3564 (for the major epimer) and 711.3567 (for the minor epimer).

Refined conditions with improved purification and handling: A solution of **23** (38.2 mg, 0.049 mmol) in anhydrous acetonitrile (250 mL) was degassed by four freeze-pump-thaw cycles and treated with $Yb(OTf)_3$ (305.66 mg, 0.49280 mmol) under argon. The resulting solution was heated to 80 °C (oil bath temperature) for 1 h. The reaction mixture was diluted with CH_2Cl_2 (250 mL) and washed with a 0.1 M aqueous solution of phosphate buffer (KH_2PO_4 and K_2HPO_4) at pH 7 (500 mL) which was cooled (ice-water bath) in advance. The organic layer was collected and the aqueous layer was re-extracted with CH_2Cl_2 (200 mL x 2). The combined organic extract was dried over Na_2SO_4, concentrated to dryness under reduced pressure, and chromatographed [RP-silica C_{18}, THF/H_2O (7:3)] to obtain two fractions. The first fraction (dark brown residue, 7.35 mg) contained **Bpheide *a*** (loss of the 2-trimethylsilyl group) and an unidentified impurity. The second fraction (purple residue, 17.35 mg, 50%) contained the title compound. The use of RP-silica and THF/H_2O (7:3) as an eluent gave much diminished formation of allomerized products. The ratio of the epimers: 1:0.1:0.1:0.2 (calculated based on integration of the ^{1}H NMR resonance from the proton at the 5-position). The characterization data (^{1}H NMR, ^{13}C{^{1}H} NMR) of the title compound were identical as above. HRMS (ESI-FTMS) (*m/z)* $[M+H]^+$ calcd for $C_{40}H_{51}N_4O_6Si$ 711.35724; found 711.35781. The values of the molar absorption coefficient in acetonitrile at room temperature were determined to be: ε = 81,000 M^{-1} cm^{-1} at λ = 360 nm, ε = 43,600 M^{-1} cm^{-1} at λ = 754 nm.

Bacteriopheophorbide *a* (Bpheide *a*). Neat TFA was degassed by bubbling with argon for 15 min. A sample of crude **24** (5.23 mg, 7.36 μmol) was treated with the neat degassed TFA (2.6 mL). The reaction mixture was stirred at room temperature for 15 min. The resulting solution was diluted with CH_2Cl_2 (20 mL) and washed with water (15 mL x 3). The organic layer was collected, and the aqueous layer was re-extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with a 5% aqueous solution of $NaHCO_3$ (50 mL x 2), dried over Na_2SO_4, and concentrated under reduced pressure, and chromatographed [RP-silica C_{18}, THF/H_2O (6:4)] to obtain blackish-purple solid (3.72 mg, 83%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.96 (s, 1H), 8.46 (s, 1H), 8.41 (s, 1H), 6.11 (s, 1H), 4.29 – 4.24 (m, 2H), 4.04 – 3.99 (m, 2H), 3.82 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H), 3.15 (s, 3H), 2.57 – 2.51 (m, 2H), 2.36 –2.28 (m, 3H), 2.23 – 2.16 (m, 1H), 2.10 – 2.01 (m, 2H), 1.78 (d, J = 7.3 Hz, 3H), 1.72 (d, J = 7.3 Hz, 3H), 1.09 (t, J = 7.4 Hz, 3H), 0.53

(br s, 1H), –0.91 (br s, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ 199.3, 189.3, 176.9, 171.3, 169.8, 169.7, 163.8, 158.2, 148.3, 139.2, 138.6, 137.0, 136.5, 133.5, 128.6, 121.4, 108.0, 99.8, 97.8, 96.0, 64.5, 55.1, 53.0, 50.7, 49.9, 49.0, 33.5, 30.8, 30.3, 30.0, 23.1, 23.0, 13.6, 11.7, 10.9. HRMS (ESI-FTMS) *m/z*: $[M–H]^-$ calcd for $C_{35}H_{37}N_4O_6$: 609.27186; found 609.27272.

Methyl bacteriopheophorbide *a* (Me-Bpheide *a*). Neat TFA was degassed by bubbling with argon for 15 min. A sample of **24** (15.37 mg, 21.63 μmol) was treated with the neat degassed TFA (7.5 mL). The solution was stirred at room temperature for 15 min. The solution was diluted with CH_2Cl_2 (200 mL) and washed with water (50 mL x 3). The organic layer was collected, and the aqueous layer was re-extracted with CH_2Cl_2 (50 mL x 2). The combined organic layer was washed with a 5% aqueous solution of $NaHCO_3$ (50 mL x 2), dried over Na_2SO_4, and concentrated under reduced pressure to obtain crude **Bpheide *a*** as a purple-black solid. Following a reported procedure,[79] the solid was dissolved in distilled THF (1.6 mL) and treated with BtOMs (51 mg, 0.23 mmol) and triethylamine (81 μL, 0.57 mmol). The resulting solution was stirred at room temperature under argon for 20 min, then a sample of MeOH (10 μL, 0.25 mmol) was added. The reaction mixture was stirred for 24 h. The solution was diluted with CH_2Cl_2 (30 mL) and washed with a 0.1 M aqueous solution of phosphate buffer (KH_2PO_4 and K_2HPO_4, pH 7, 100 mL). The organic layer was collected, and the aqueous layer was re-extracted with CH_2Cl_2 (20 mL x 2). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [RP-C_{18} silica, THF/H_2O (7:3)] to afford a purple solid (9.73 mg, 72%). ^1H NMR ($CDCl_3$, 700 MHz) δ 8.98 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 6.08 (s, 1H), 4.31 – 4.23 (m, 2H), 4.05 – 4.00 (m, 2H), 3.85 (s, 3H), 3.59 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 3.16 (s, 3H), 2.58 – 2.52 (m, 1H), 2.51 – 2.46 (m, 1H), 2.37 – 2.32 (m, 1H), 2.27 – 2.21 (m, 1H), 2.09 – 2.04 (m, 1H), 2.03 – 1.99 (m, 1H), 1.79 (d, J = 7.4 Hz, 3H), 1.73 (d, J = 7.5 Hz, 3H), 1.11 (t, J = 7.3 Hz, 3H), 0.49 (br s, 1H), –0.95 (br s, 1H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$) δ 199.3, 189.2, 173.5, 171.2, 169.7, 169.7, 163.8, 158.1, 148.2, 138.5, 137.0, 136.4, 128.8, 121.5, 108.1, 99.8, 97.8, 95.9, 64.5, 55.1, 53.0, 51.8, 50.7, 49.8, 49.0, 33.5, 31.1, 30.3, 30.1, 23.1, 23.0, 13.6, 11.7, 10.9. HRMS (ESI-FTMS) $[M+H]^+$ calcd for $C_{36}H_{41}N_4O_6$: 625.30206; found 625.30279.

Bacteriopheophytin *a* (Bpheo *a*). Neat TFA was degassed by bubbling with argon for 15 min. A sample of **24** (7.25 mg, 10.2 μmol) was treated with the neat degassed TFA (2.6 mL). The solution was stirred at room temperature for 15 min. The solution was diluted with CH_2Cl_2 (200 mL) and washed with water (50 mL x 3). The organic layer was collected, and the aqueous layer was re-extracted with CH_2Cl_2 (50 mL x 2). The combined organic layer was washed with a 5% aqueous solution of $NaHCO_3$ (50 mL x 2), dried over Na_2SO_4, and concentrated under reduced pressure to obtain crude **Bpheide *a*** as a purple-black solid. Following a reported procedure,[79] the solid was dissolved in distilled THF (0.8 mL) and treated with BtOMs (24 mg, 0.11 mmol) and triethylamine (38 μL, 0.27 mmol). The resulting solution was stirred at room temperature under argon for 20 min, then a sample of native phytol (40 μL, 0.11 mmol) was added. The reaction mixture was stirred for 24 h. The solution was diluted with CH_2Cl_2 (30 mL) and washed with an aqueous solution of 0.1 M phosphate buffer (KH_2PO_4 and K_2HPO_4, pH 7, 100 mL). The organic

layer was collected, and the aqueous layer was re-extracted with CH_2Cl_2 (20 mL x 2). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [RP-C_{18} silica, THF/H_2O (7:3)] to afford a purple solid (5.91 mg, 65%) with diastereomeric ratio 1: 0.04:0.06:0.16 based on the integration of the resonance from the proton at the 5-position. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.99 (s, 1H), 8.49 (s, 1H), 8.42 (s, 1H), 6.10 (s, 1H), 5.21 – 5.17 (m, 1H), 4.54 – 4.45 (m, 2H), 4.30 – 4.27 (m, 2H), 4.06 – 4.02 (m, 2H), 3.86 (s, 3H), 3.50 (s, 3H), 3.46 (s, 3H), 3.17 (s, 3H), 2.58 – 2.52 (m, 1H), 2.49 – 2.43 (m, 1H), 2.38 – 2.32 (m, 1H), 2.31 – 2.36 (m, 1H), 2.23 – 2.17 (m, 1H), 2.11 – 2.05 (m, 1H), 1.93 – 1.89 (m, 2H), 1.79 (d, J = 7.4 Hz, 3H), 1.72 (d, J = 7.5 Hz, 3H), 1.60 (s, 3H), 1.50 (dt, J = 13.3, 6.6 Hz, 1H), 1.36 – 0.98 (m, 22H), 0.86 – 0.84 (m, 6H), 0.82 – 0.79 (m, 6H), 0.46 (br s, 1H), –0.97 (br s, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 199.3, 189.2, 173.1, 171.2, 169.7, 163.8, 158.1, 148.2, 143.1, 139.2, 138.4, 136.9, 136.4, 133.4, 128.8, 121.5, 117.9, 108.2, 99.8, 97.8, 95.9, 64.5, 61.6, 55.1, 52.9, 50.8, 49.9, 49.0, 40.0, 39.5, 37.52, 37.46, 37.4, 36.8, 33.5, 32.9, 32.8, 31.2, 30.3, 30.0, 28.1, 25.1, 24.9, 24.6, 23.1, 23.0, 22.85, 22.76, 19.9, 19.8, 16.4, 13.6, 11.7, 10.9. HRMS (ESI-FTMS) $[M]^+$ calcd for $C_{55}H_{76}N_4O_6$: 888.57594, found: 888.57589.

Bacteriochlorophyll *a* (BChl *a*). 2,2,6,6-Tetramethylpiperidine was distilled over NaOH and degassed by four freeze-pump-thaw cycles; thiophene was distilled over potassium and degassed by four freeze-pump-thaw cycles; distilled Et_2O was degassed by four freeze-pump-thaw cycles; and all glassware was dried in the oven and flushed with argon. Followed a reported procedure[82] with modifications, a solution of 2,2,6,6-tetramethylpiperidine (51 μL, 0.30 μmol) in distilled Et_2O (300 μL) was treated with a solution of *n*-BuLi (150 μL, 1.6 M in hexanes, 0.24 μmol) at 0 °C (ice-water bath) and allowed to stir at room temperature for 15 min to obtain a solution A. A solution of 2,6-di-*tert*-butylhydroxytoluene (BHT, 61 mg, 0.28 mmol) in distilled thiophene (4 mL) was treated with a solution of CH_3MgI (85 μL, 3 M in Et_2O, 0.26 mmol) at 0 °C (ice-water bath) and allowed to stir at room temperature for 15 min to obtain a solution B. The solution A (28 μL) was mixed with solution B (270 μL), and the resulting mixture was treated with a solution of **Bpheo *a*** (1.0 mg, 1.1 μmol) in thiophene (85 μL). The reaction mixture was stirred for 30 min at room temperature, quenched by the addition of a 0.1 M aqueous solution of phosphate buffer (KH_2PO_4 and K_2HPO_4, pH 7, 2 mL), and the suspension was extracted with Et_2O (1 mL x 3). The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed [RP-C_{18} silica, acetonitrile/MeOH (95:5)] to obtain the title compound (0.3 mg, 30%). MALDI-MS data: m/z = 910.65 $[M]^+$ with use of DAN as a matrix.

II. References

S1 Bruker, Bruker APEX5, Bruker AXS Inc., Madison, Wisconsin, USA, 2023.

S2 Bruker, Bruker SAINT, Bruker AXS Inc., Madison, Wisconsin, USA, 2023.

S3 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3–8.

S4 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339–341.

III. Synthesis of nitroalkenes

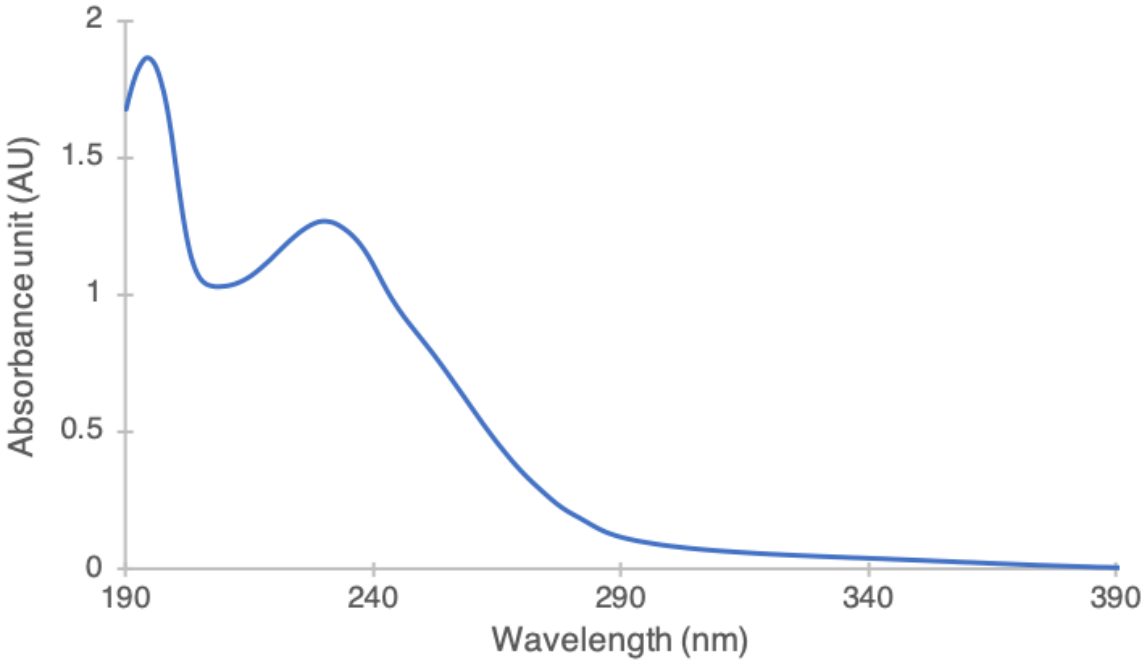


Fig. S1. Absorption spectrum of nitroalkene **1** in acetonitrile at room temperature.

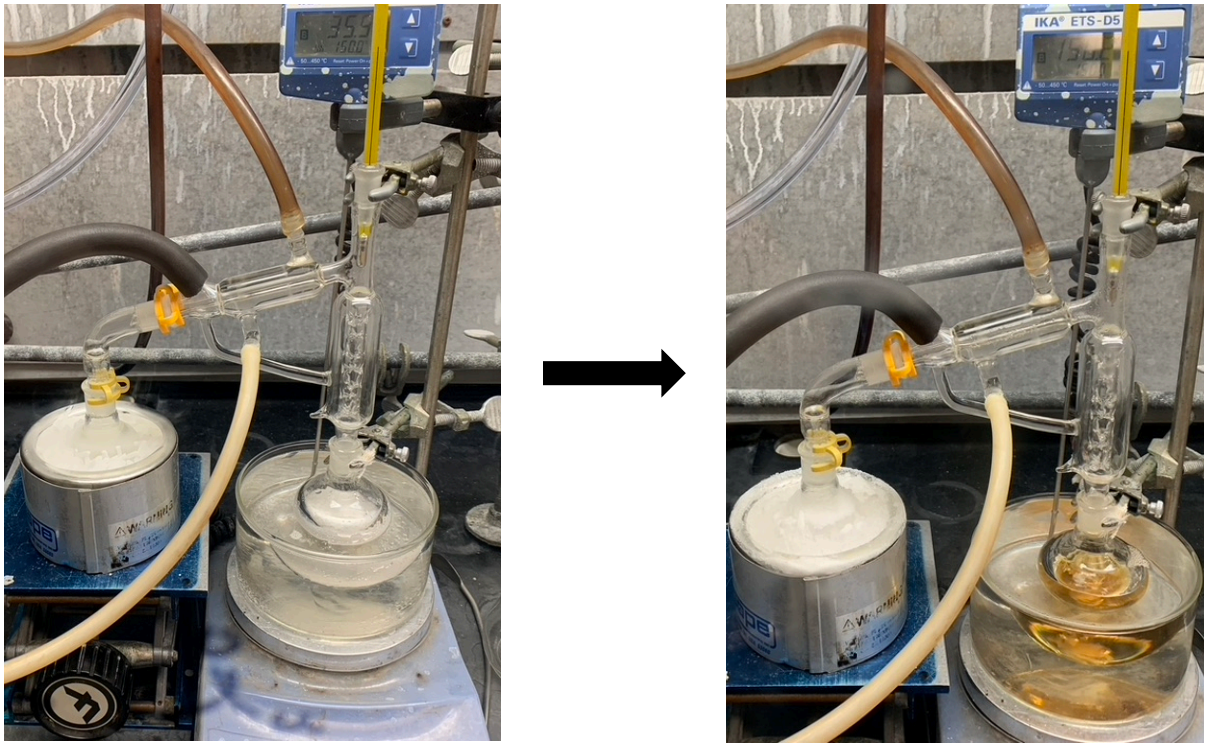


Fig. S2. Experimental apparatus for the synthesis of nitroalkene **3**. The left photo shows the inception of step 2 wherein the suspension containing the nitroalcohol (crude material from step 1) is heated in an oil bath at 150–160 °C; the nitroalkene and water are collected in the flask immersed in a dry ice-acetone bath (–78 °C). The right photo shows the ongoing step 2 wherein the suspension has dissolved to yield a clear, light-brown solution.

IV. Studies of the asymmetric Michael reaction

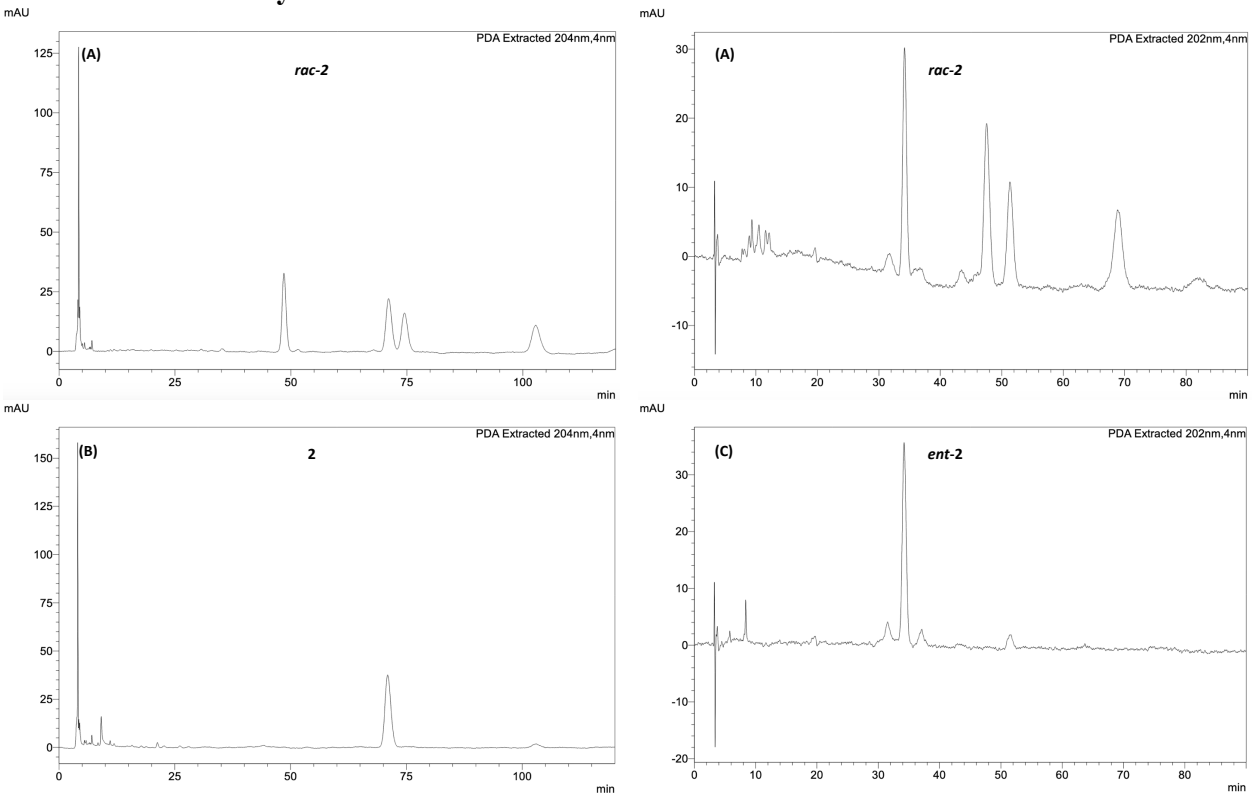


Fig. S3. Product distribution upon chiral HPLC analysis of the Michael reaction of nitroalkene **1** and propanal. (A) Upon use of pyrrolidine (displayed twice for comparison), to afford the mixture of stereoisomers (***rac*-2**). (B) Upon use of the chiral catalyst **I** to obtain the desired target **2**. (C) Upon use of the chiral catalyst **II** to obtain the enantiomer of the target (i.e., ***ent*-2**) for chromatographic identification.

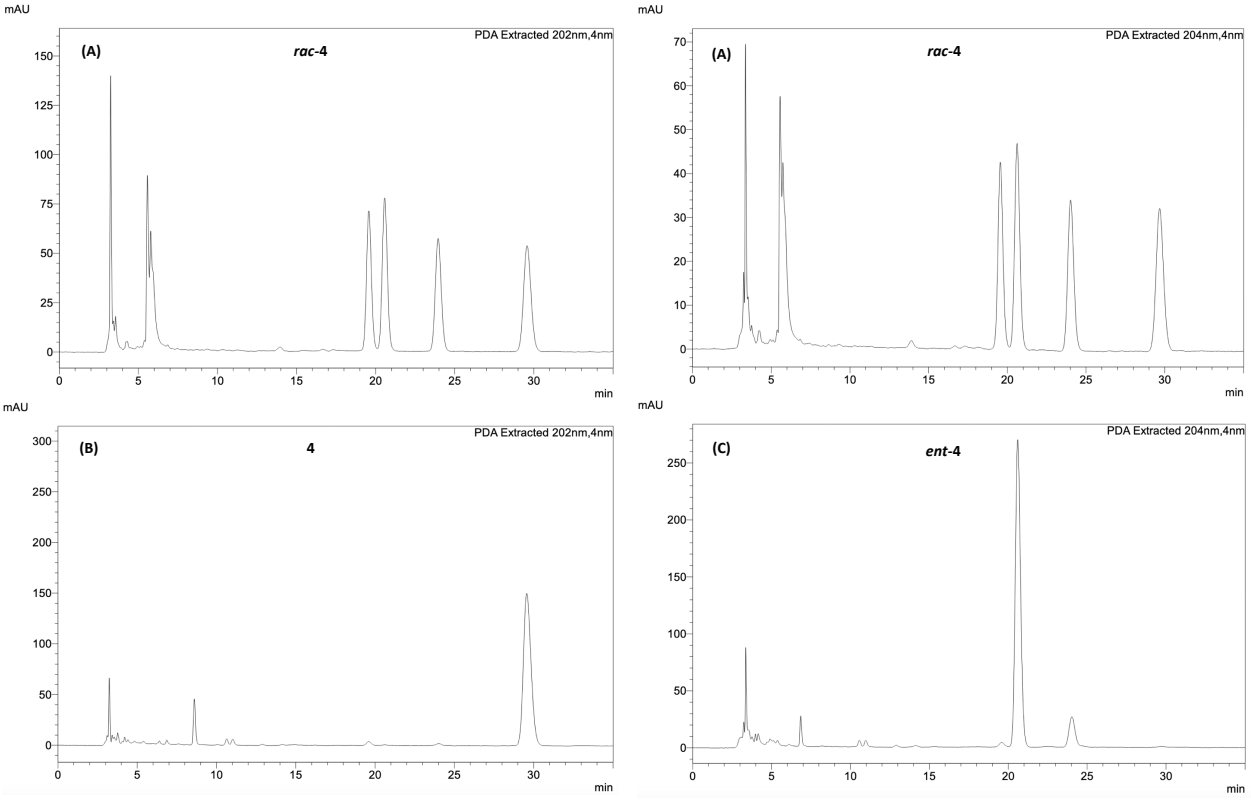


Fig. S4. Product distribution upon chiral HPLC analysis of the Michael reaction of nitroalkene **3** and butanal. (A) Upon use of pyrrolidine (displayed twice for comparison), to afford the mixture of stereoisomers (***rac*-4**). (B) Upon use of the chiral catalyst **II** to obtain the desired target **4**. (C) Upon use of the chiral catalyst **I** to obtain the enantiomer of the target (i.e., ***ent*-4**) for chromatographic identification.

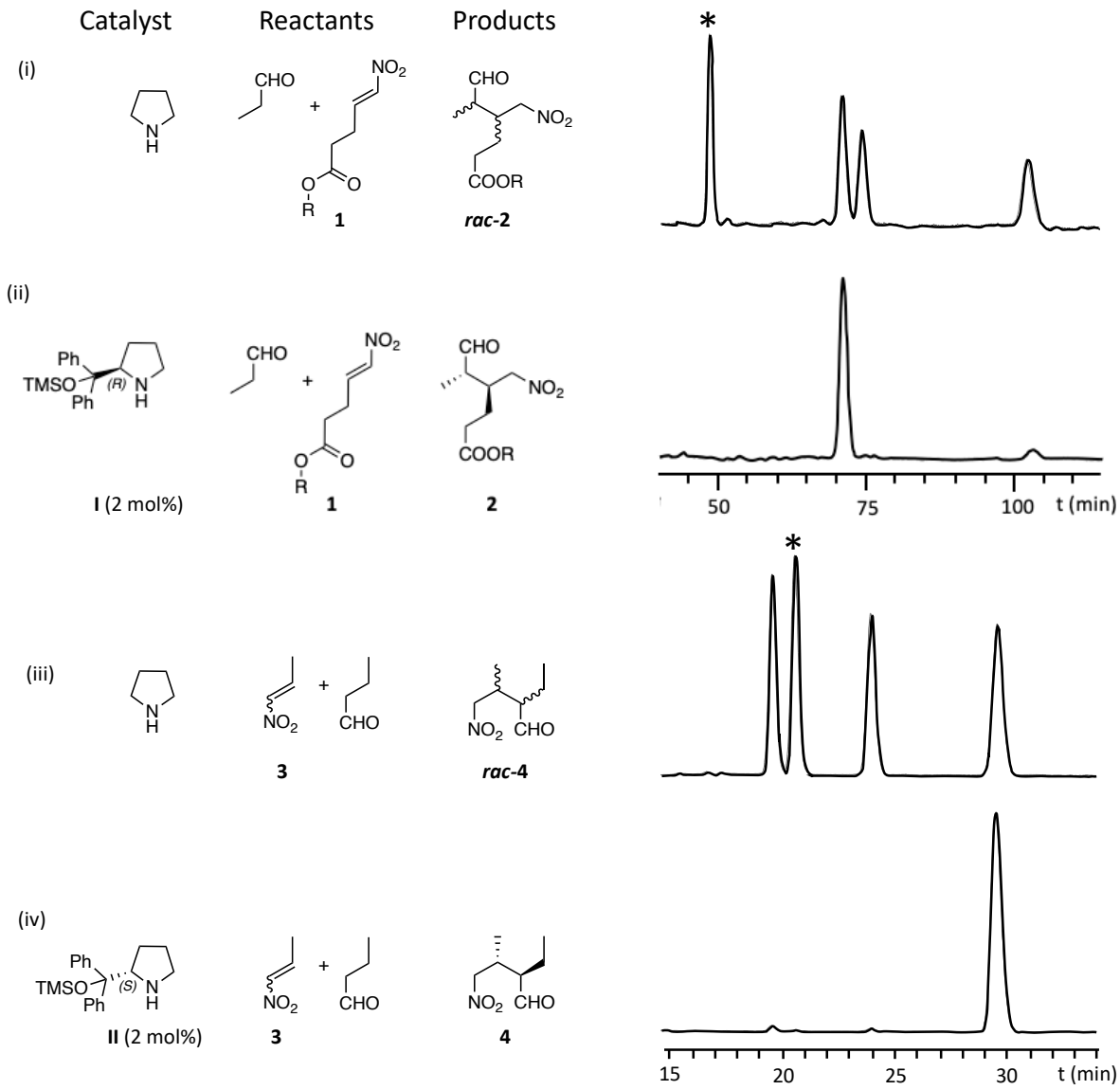


Fig. S5. Michael reaction studies examined via chiral HPLC with far-UV detection. The asterisk indicates the enantiomer in each case. See the Experimental Section for conditions.

V. Data for the AD and BC halves and precursors

V.1. SCXRD data for compound 5

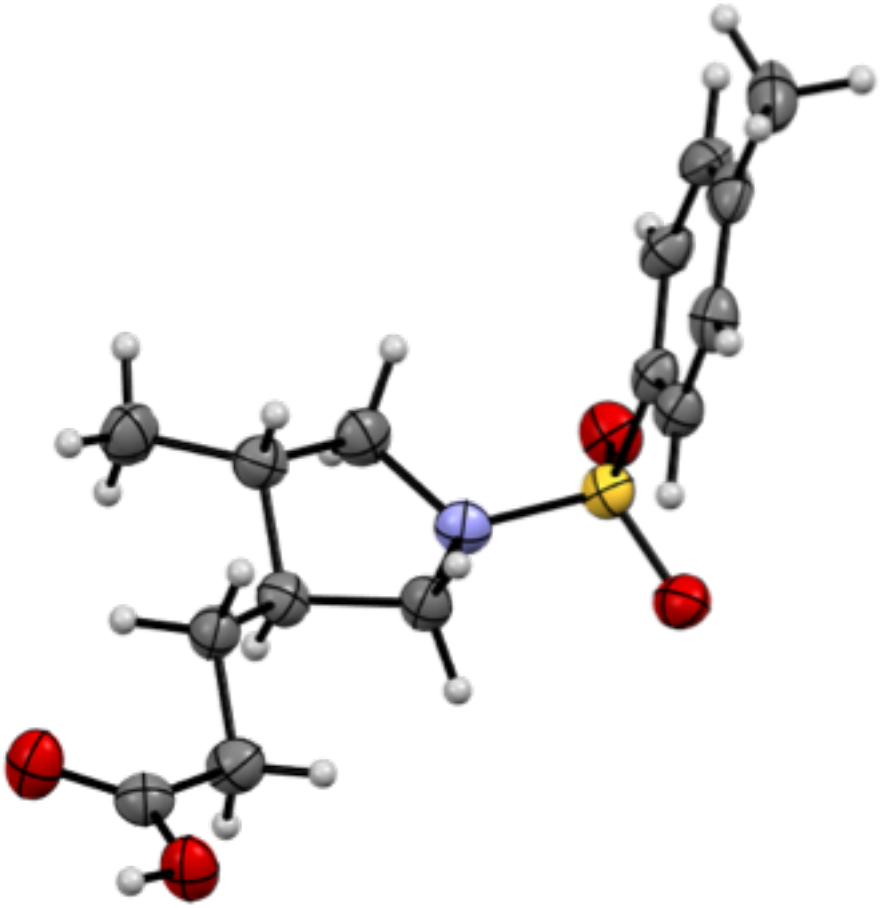


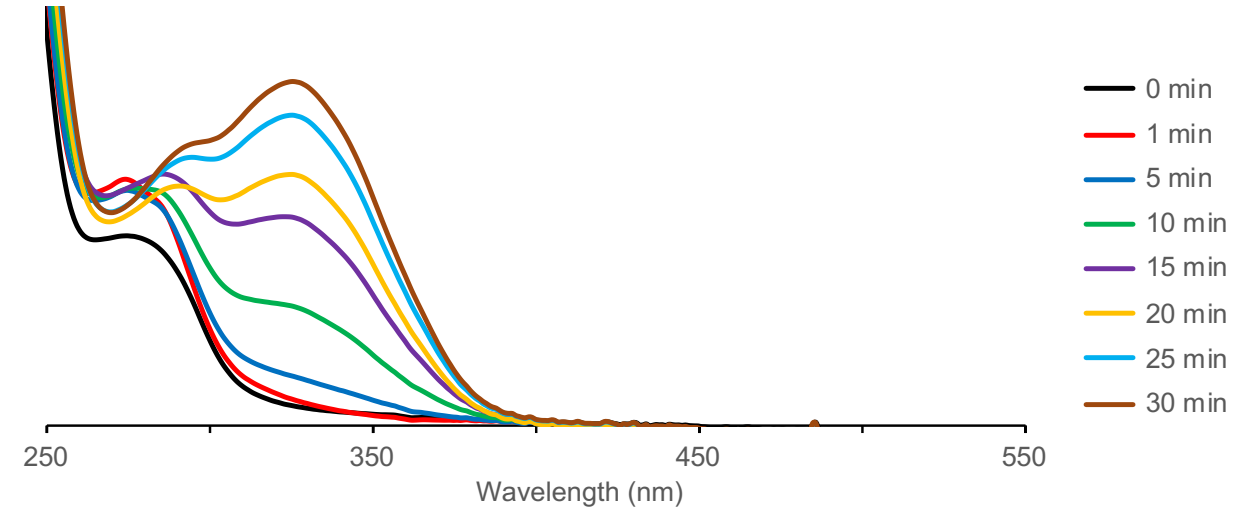
Fig. S6. Single-crystal structure of pyrrolidine **5** with thermal ellipsoids drawn at the 50% probability level. Atom colors: C = grey, N = blue, O = red, S = yellow, and H = white).

Table S1 Single-crystal X-ray structure data for pyrrolidine **5**

CCDC registry	2519172
Empirical formula	$C_{15}H_{21}NO_4S$
Formula weight	311.39
Temperature/K	100
Crystal system	Monoclinic
Space group	P 2_1
a/Å	12.0469(13)
b/Å	7.654(1)
c/Å	17.8313(19)
α/°	90
β/°	103.462(6)
γ/°	90
Volume/Å^3	1599.0(3)
Z	4
ρ_{calc} (g/cm^3)	1.293
μ/mm^{-1}	1.93
F(000)	664
Crystal size/mm^3	0.66 × 0.21 × 0.03
Radiation	CuKα
2θ range for data collection/°	6.3 to 68.2
Index ranges	$-14 \leq h \leq 14$, $-9 \leq k \leq 8$, $-21 \leq l \leq 21$
Reflections collected	9432
Independent reflections	5285 [R_{int} = 0.0512, R_{sigma} = 0.0715]
Data/restraints/parameters	5285/1/407
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0504, wR_2 = 0.1170
Final R indexes [all data]	R_1 = 0.0627, wR_2 = 0.1287
Largest diff. peak/hole / e Å^{-3}	0.53, −0.27

V.2. Paal-Knorr and IBX-oxidation reaction data

(A)



(B)

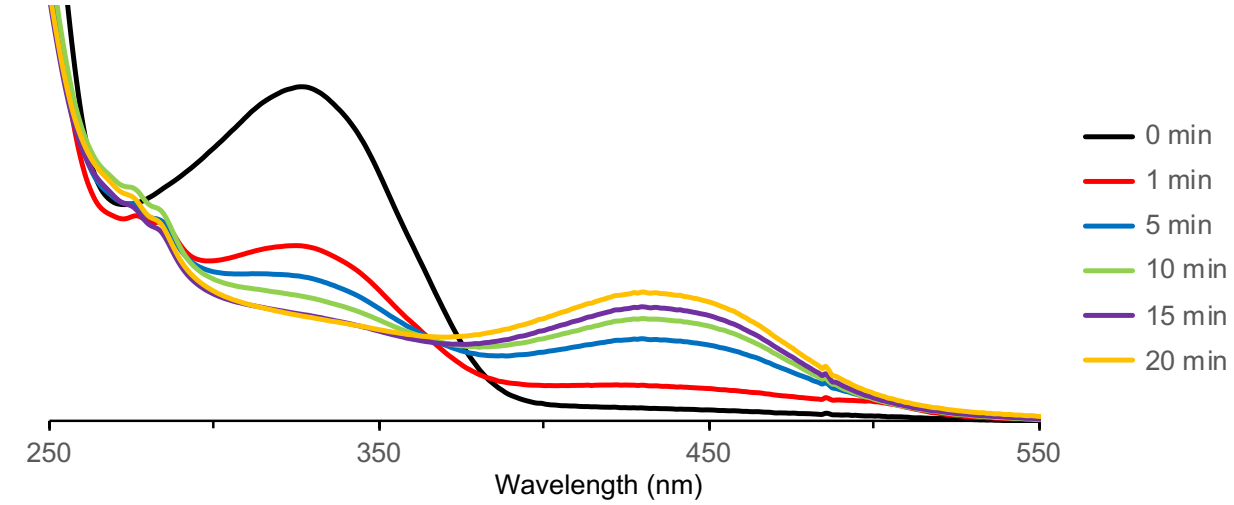


Fig. S7. Panel A: spectral evolution in the conversion of **11** to **12** upon treatment to Paal-Knorr type cyclization (spectra in acetonitrile at room temperature; 0–30 min). Panel B: the conversion of **12** to **13** upon treatment with IBX in acetonitrile at room temperature (0–20 min).

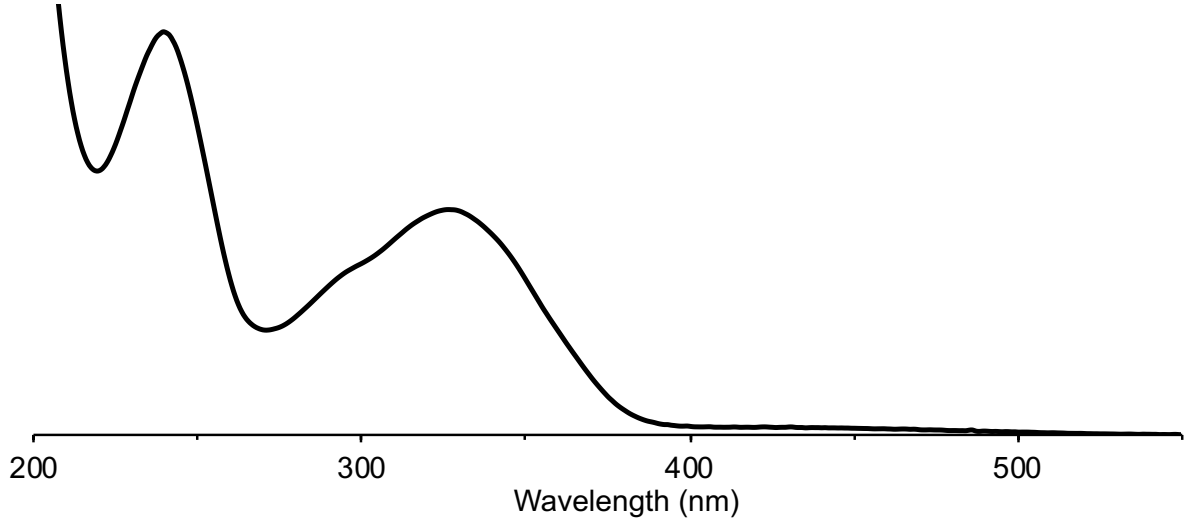


Fig. S8. Absorption spectrum of compound **12** in acetonitrile at room temperature.

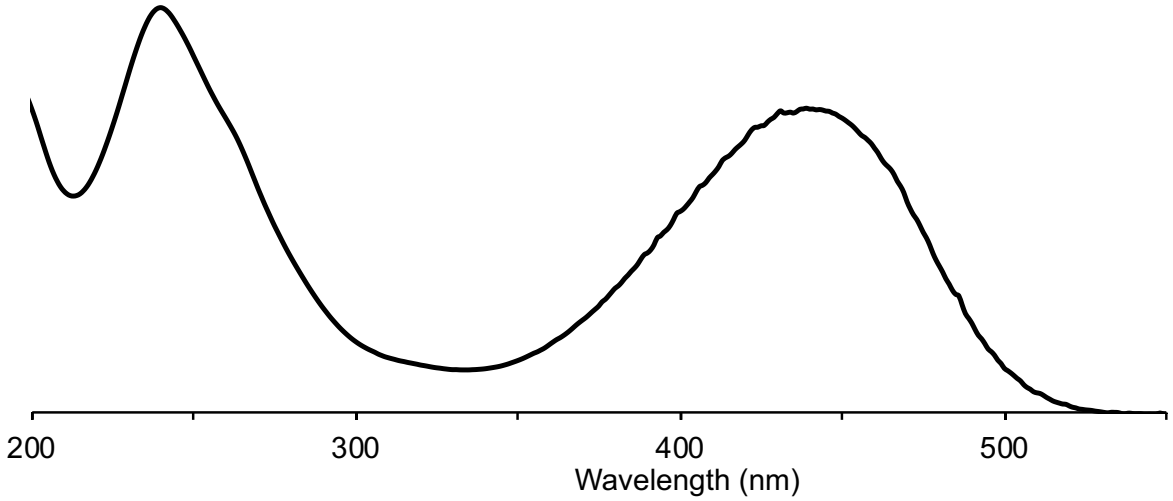


Fig. S9. Absorption spectrum of compound **13** in acetonitrile at room temperature.

V.3. SCXRD data for compounds 16a and 16b

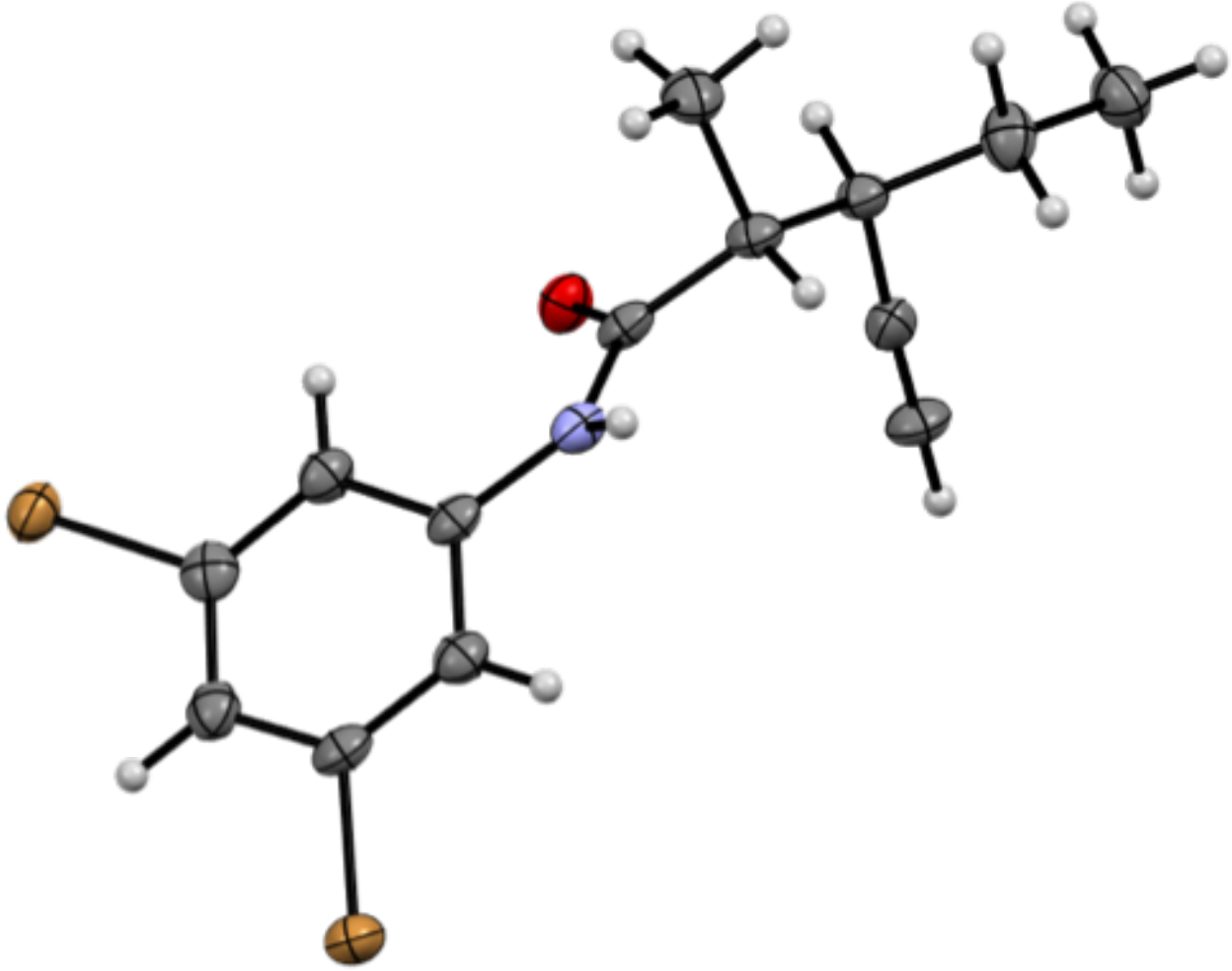


Fig. S10a. Single-crystal structure of pentynamide **16a** with thermal ellipsoids drawn at the 50% probability level. Atom colors: C = grey, N = blue, O = red, Br = brown, and H = white).

Table S2a Single-crystal X-ray structure data for pentynamide **16a**

CCDC registry	2519171
Empirical formula	$C_{14}H_{15}Br_2NO$
Formula weight	373.09
Temperature/K	100
Crystal system	Monoclinic
Space group	P 2_1
a/Å	4.9130(6)
b/Å	11.0001(14)
c/Å	13.3169
α/°	90
β/°	93.040(5)
γ/°	90
Volume/Å^3	718.68(16)
Z	2
ρ_{calc} (g/cm^3)	1.724
μ/mm^{-1}	7.05
F(000)	368
Crystal size/mm^3	0.32 × 0.13 × 0.03
Radiation	CuKα
2θ range for data collection/°	3.3 to 68.2
Index ranges	$-5 \leq h \leq 5$, $-13 \leq k \leq 11$, $-16 \leq l \leq 16$
Reflections collected	9414
Independent reflections	2522 [R_{int} = 0.0513, R_{sigma} = 0.0462]
Data/restraints/parameters	2522/1/169
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0331, wR_2 = 0.0859
Final R indexes [all data]	R_1 = 0.0345, wR_2 = 0.0870
Largest diff. peak/hole / e Å^{-3}	1.02, −0.49

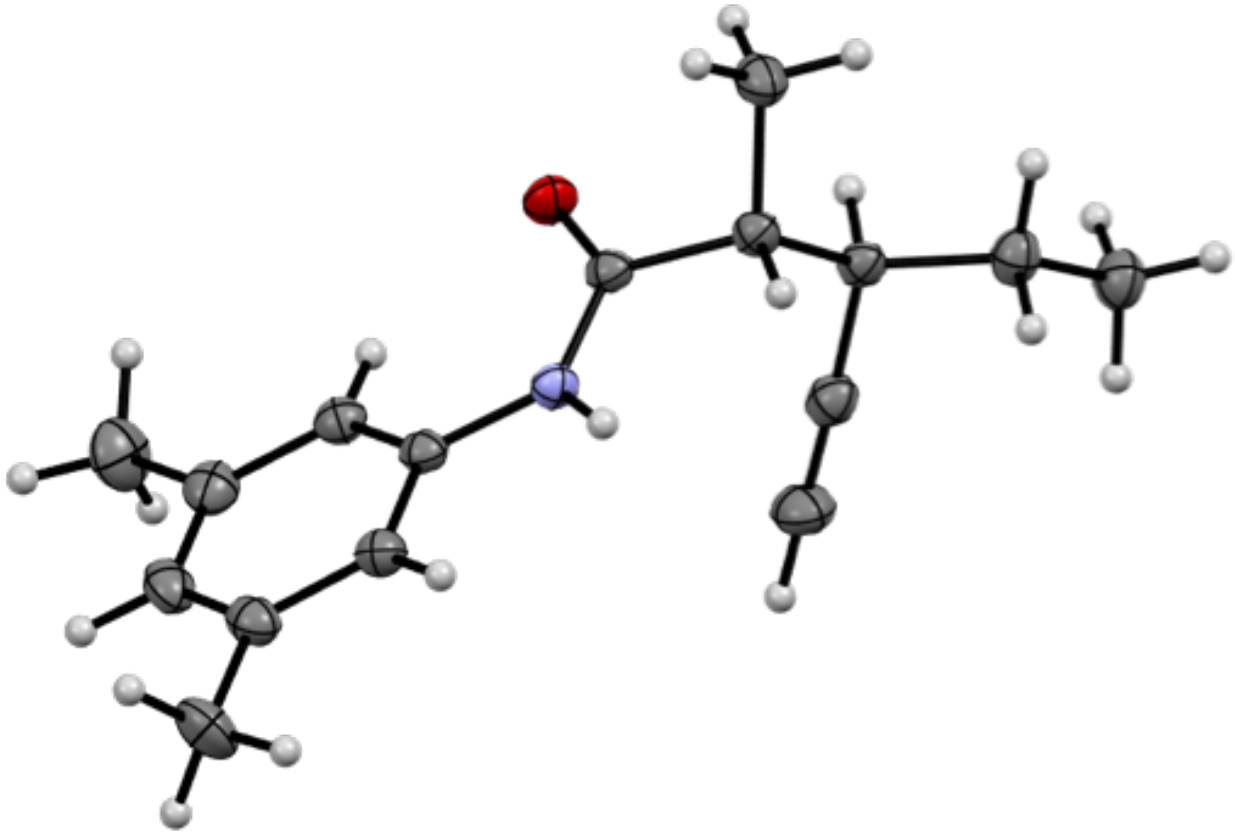


Fig. S10b. Single-crystal structure of pentynamide **16b** with thermal ellipsoids drawn at the 50% probability level. Atom colors: C = grey, N = blue, O = red, and H = white).

Table S2b Single-crystal X-ray structure data for pentynamide **16b**

CCDC registry	2519170
Empirical formula	$C_{16}H_{21}NO$
Formula weight	243.34
Temperature/K	100
Crystal system	Monoclinic
Space group	P 2_1
a/Å	9.5441(12)
b/Å	14.821(2)
c/Å	11.1946(15)
α/°	90
β/°	111.271(4)
γ/°	90
Volume/Å^3	1475.6(3)
Z	4
ρ_{calc} (g/cm^3)	1.095
μ/mm^{-1}	0.523
F(000)	528
Crystal size/mm^3	0.41 × 0.20 × 0.06
Radiation	CuKα
2θ range for data collection/°	5.0 to 67.4
Index ranges	$-11 \leq h \leq 11$, $-17 \leq k \leq 17$, $-13 \leq l \leq 13$
Reflections collected	30070
Independent reflections	5282 [R_{int} =0.0458, R_{sigma} = 0.0299]
Data/restraints/parameters	5282/1/341
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0354, wR_2 = 0.0920
Final R indexes [all data]	R_1 = 0.0361, wR_2 = 0.0933
Largest diff. peak/hole / e Å^{-3}	0.14, −0.16

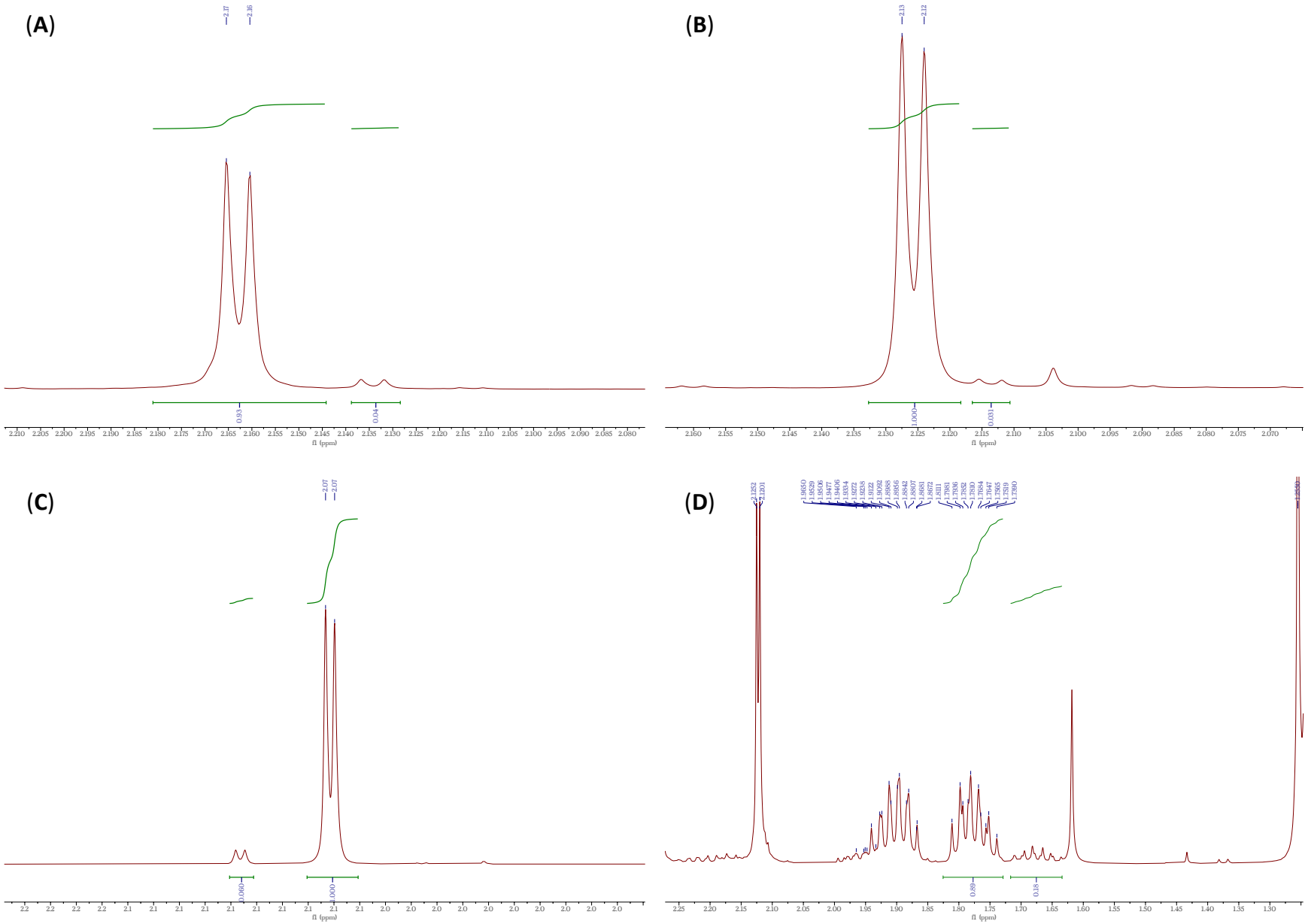


Fig. S11. [1]H NMR spectra to assess the presence of diastereomers. Panels A–D are from compounds **14**, **15**, **19**, and **6**, respectively.

VI. The Knoevenagel reaction

Table S3 Study of conditions for the Knoevenagel reaction[a]

Entry	**13** : **22** (mg) concentration	Conditions	Product	TLC analysis		Source
				AD half	BC half	
1	62.5 : 56.5 0.040 M	piperidine/AcOH (15 mM/15 mM in CH_3CN, 3.75 mL), 3 Å MS (60.34 mg)	13.1 mg 10%[c]	decomposed	remained	Ref. 66
2	1 : 0.9 0.096 M	D, L-tryptophan (0.15 mg) DMSO (25 μL)	None[d]	decomposed	remained	Ref. 71
3	1 : 0.9 0.048 M	Pro-β-Ala (0.45 mg) MeOH (50 μL)	Small amount[d]	decomposed	remained	Ref. 70
4	1 : 0.9 0.048 M	Piperidine (0.12 μL) MeOH (50 μL)	None[d]	decomposed slowly	remained	Ref. 73
5	1 : 0.9 0.048 M	Pro-β-Ala (0.45 mg) LiCl (0.1 mg), MeOH (50 μL)	Small amount[d]	decomposed	remained	Ref. 70
6	1 : 0.9 0.048 M	Lithium prolinate (0.29 mg) MeOH (50 μL)	None[d]	decomposed slowly	remained	Ref. 69
7	1 : 0.9 0.048 M	Pro-β-Ala (0.45 mg) EtOH (50 μL)	1:10 ratio with BC[e]	decomposed	remained	Ref. 70
8	1 : 0.9 0.048 M	Pyrrolidinium acetate (10 μL) LiBr (tip of spatula), CH_2Cl_2 (50 μL)	3:10 ratio with BC[e]	decomposed	remained	Ref. 72
9	50.2 : 46.3 0.083 M	Pyrrolidinium acetate[b] (0.25 mL) LiBr (5 mg), CH_2Cl_2 (1.2 mL)	25.9 mg 27%[c]	decomposed	remained	Ref. 72
10	20.7 : 19.0 0.083 M	Pyrrolidinium acetate[b] (0.1 mL) LiBr (2 mg), CH_2Cl_2 (0.5 mL)	9.55 mg 25%[c]	decomposed	remained	Ref. 72
11	126.9 : 125.1 0.19 M	Pyrrolidinium acetate[b] (0.6 mL) $Mg(OTf)_2$ (120.1 mg), CH_2Cl_2 (10 mL)	85.1 mg 35%[c]	decomposed	remained	here

[a]All of the reactions used anhydrous solvents and were carried out under argon in the dark. [b]The ionic liquid was degassed by bubbling with argon for 15 min in prior. [c]Isolated yield. [d]By TLC analysis. [e]By ^{1}H NMR analysis of the product versus remaining BC half.

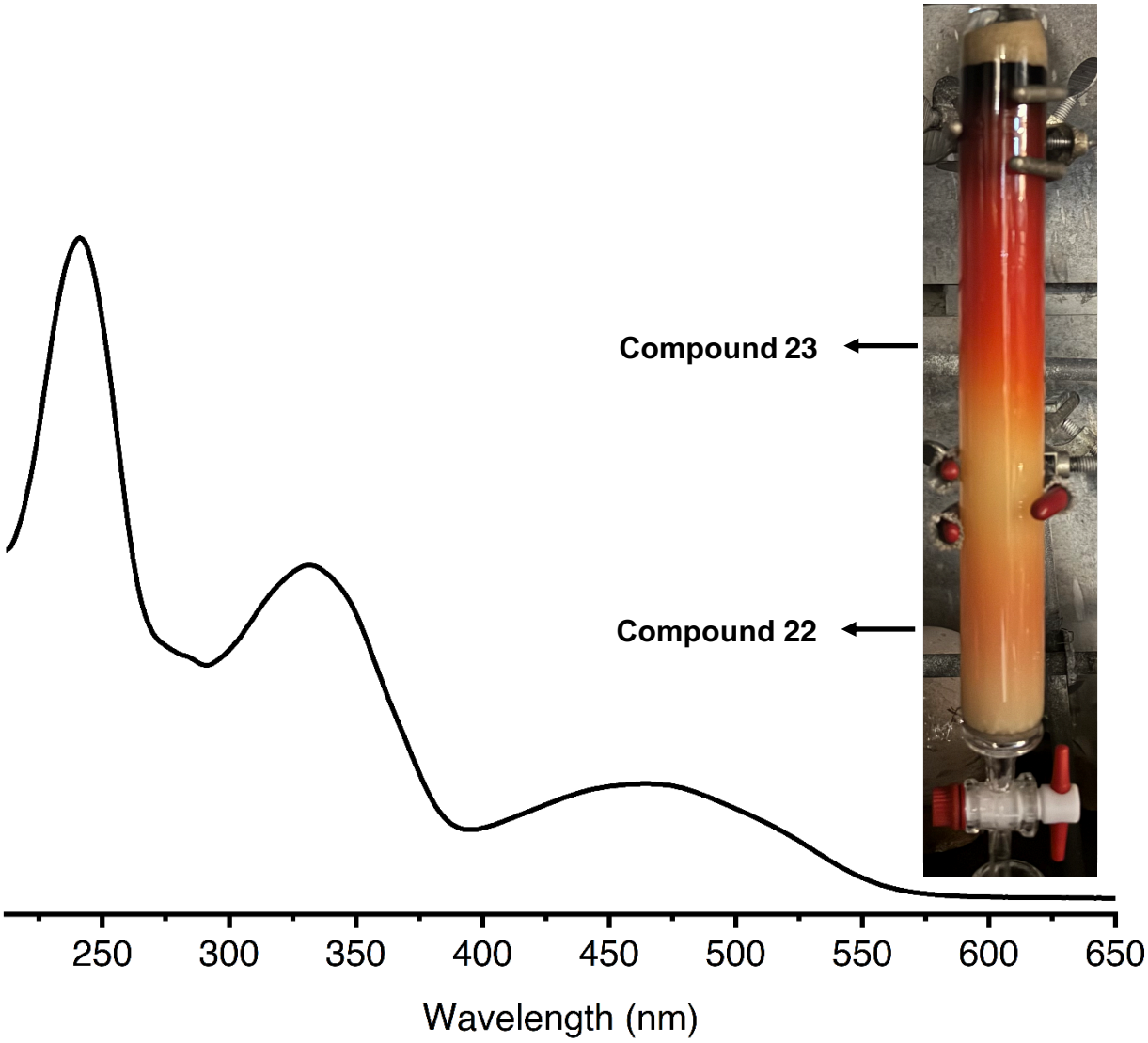


Fig. S12. Absorption spectrum of Knoevenagel product **23** in acetonitrile at room temperature. The inset photo shows the column chromatography of the reaction mixture: the orange band is the Knoevenagel product **23**.

VII. Epimer fractionation

Compound **24** was subjected to preparative TLC, which afforded two fractions, **fraction 1a** and **fraction 1b**. Both fractions contained two epimers but in different ratios. Analysis by RP-HPLC with absorption spectral detection (746 nm) showed the composition of **fraction 1a** to be slightly enriched in the 13^2(*S*) epimer (62%) versus the 13^2(*R*) epimer (38%). On the other hand, **fraction 1b** was highly enriched in the 13^2*(R)* epimer (94%). Analysis of the two samples (at low concentration in acetonitrile) stored at –20 °C for 10 days indicated hardly any epimerization. The samples at –20 °C were in solution (note that the mp of acetonitrile is –45 °C).

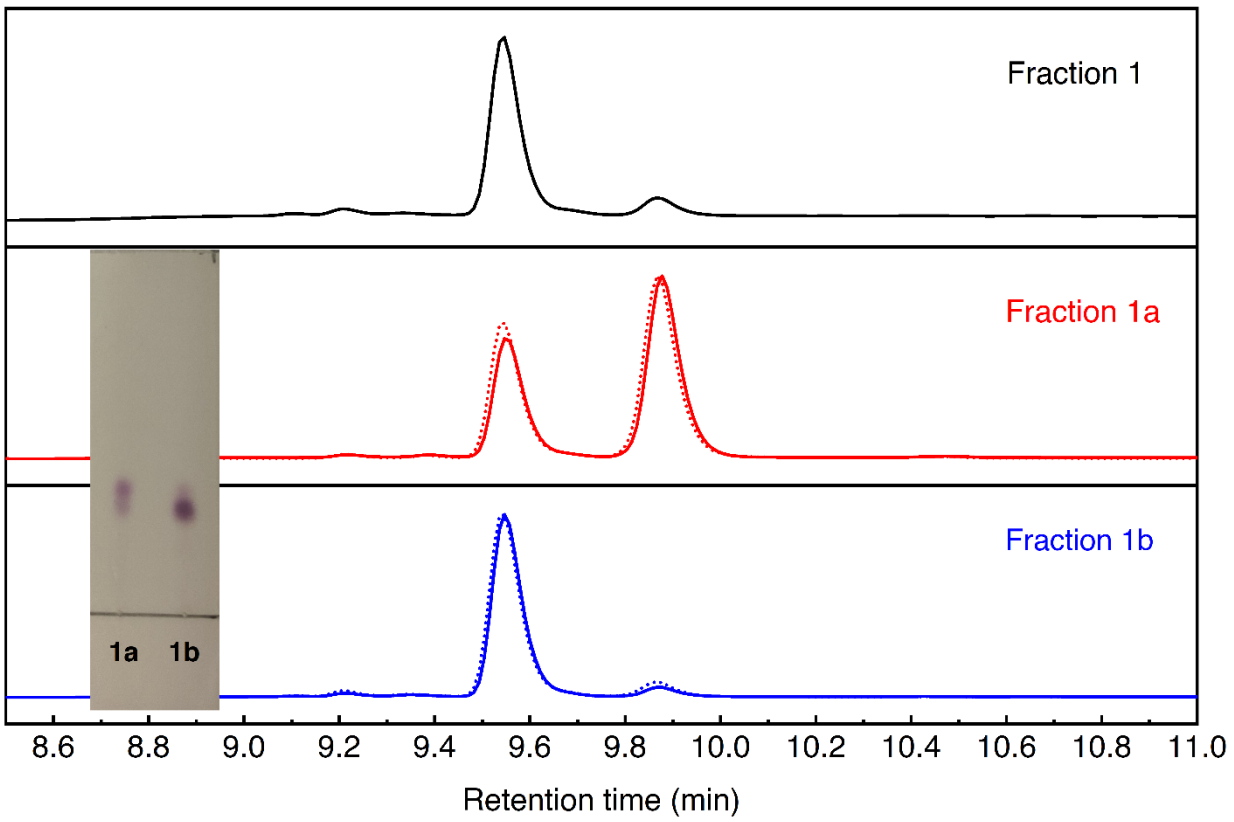


Fig. S13. RP-HPLC traces with λ_{det} = 746 nm of fractions of compound **24** (see Experimental Section for conditions). Top panel: Fraction #1 (top) containing two epimers, 13^2(*R*) and 13^2(*S*), in 91:9 ratio (black solid line). Middle panel: **Fraction 1a** containing 13^2(*R*) and 13^2(*S*) epimers in 38:62 ratio (upon chromatographic isolation from fraction 1, red solid line) and 41:59 ratio (after storage in acetonitrile for 10 days at –20 °C, red dotted line). Bottom panel: **fraction 1b** containing 13^2(*R*) and 13^2(*S*) epimers in 94:6 ratio (upon chromatographic isolation from fraction 1, blue solid line) and 93:7 ratio (after storage in acetonitrile for 10 days at –20 °C, blue dotted line). A photo of a silica TLC plate of fractions 1a and 1b is shown at left.

VIII. Sensitivity of the macrocycles to routine laboratory handling

Photobleaching and allomerization are characteristic features of members of the chlorophyll and bacteriochlorophyll family. In the first trial of the double-ring closure of **23**, the crude reaction mixture was purified by column chromatography [silica, hexanes/ethyl acetate (2:1)] as eluant to obtain the first fraction (*1*) comprised compound **24**. Ultimately, three remaining fractions [eluted by CH_2Cl_2/MeOH (20:1)] were collected in trace amounts and characterized by absorption spectroscopy and MALDI-MS analysis. The structures of the compounds in fractions *2–4* were proposed provisionally solely on the basis of absorption and MALDI-MS analysis. The results show the critical importance of avoiding silica gel, light, and air for safe handling.

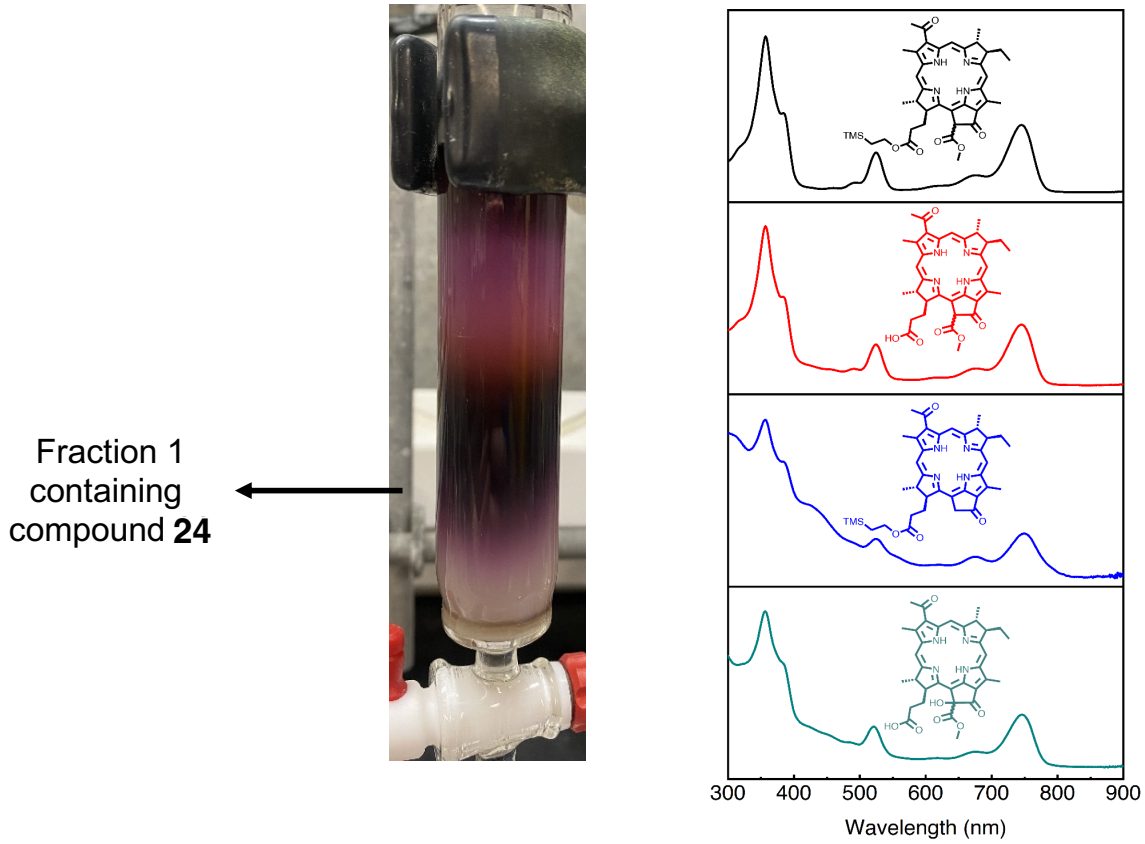


Fig. S14. The absorption spectrum of fractions *1–4* (from top to bottom). The inset photo shows the column chromatography of the reaction mixture, where the dark purple band is the product **24**.

IX. Exploratory cleavage of the 2-(trimethylsilyl)ethyl protecting group

With TBAF solution in THF: A quantity of **24** (0.185 mg, 0.26 μmol) was taken from a stock solution in CH_2Cl_2 and placed in a 0.3 mL conical vial. The solvent was allowed to evaporate under a stream of argon followed by the addition of freshly distilled THF (50 μL) and TBAF reagent (1 M solution in THF, 50 μL), whereupon the purple solution immediately turned green, consistent with formation of the chlorin macrocycle.

With TBAF supported on silica: A quantity of **24** (0.185 mg, 0.26 μmol) was taken from a stock solution in CH_2Cl_2 and placed in a 0.3 mL conical vial. The solvent was allowed to evaporate under a stream of argon followed by the addition of TBAF supported on silica (~1.5 mmol/g, 21.03 mg) and freshly distilled THF (100 μL). The reaction mixture was stirred at room

temperature for 1 h. A reaction aliquot of 10 µL was taken after 1 h, diluted in acetonitrile (0.5 mL), and analyzed by RP-HPLC. No reaction was observed.

With 5% TFA in CH_2Cl_2: A quantity of **24** (0.185 mg, 0.26 µmol) was taken from a stock solution in CH_2Cl_2 and placed in a 0.3 mL conical vial. The solvent was allowed to evaporate under a stream of argon followed by the addition of 5% (w/w) TFA in CH_2Cl_2 (100 µL). The reaction mixture was stirred at room temperature for 3 h. An aliquot of 10 µL was taken from the reaction mixture at various timepoints, diluted in acetonitrile (0.5 mL), and analyzed by RP-HPLC-UV/Vis-MS. The reaction barely proceeded at room temperature. Thus, the reaction vial was replenished with an additional amount of CH_2Cl_2 (100 µL). After stirring overnight at 40 °C, analysis by RP-HPLC indicated the presence of multiple products derived from allomerization and oxidation processes (Fig. S15).

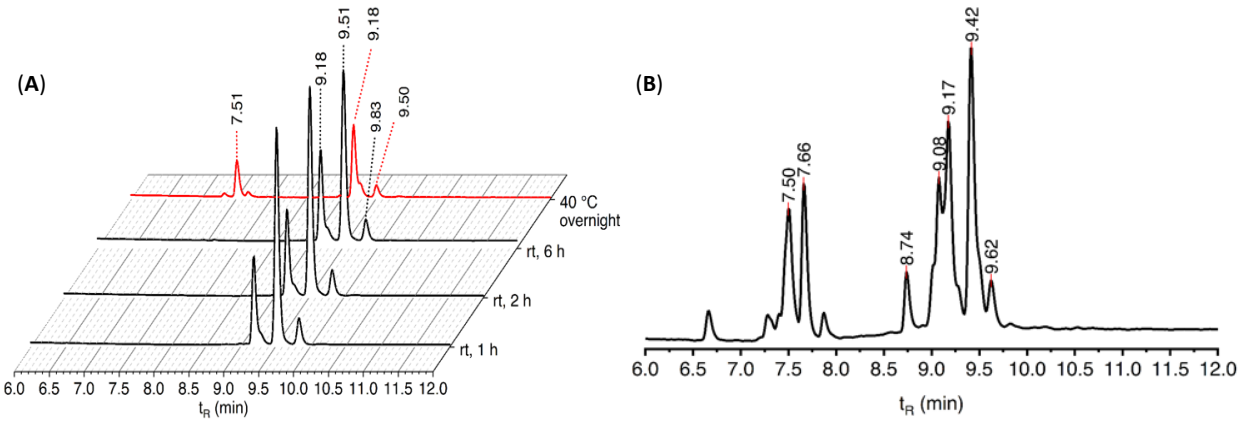


Fig. S15. RP-HPLC analysis of reaction aliquots upon treatment of **24** with 5% TFA (w/w) in CH_2Cl_2 (see Experimental Section for conditions). (A) Traces (λ_{det} = 745 nm) from reactions at room temperature (black traces) or 40 °C (red trace). The peaks at 7.51 and 9.18 min in the red trace are assigned to 13^2-hydroxybacteriochlorins termed **Bpheide *a*-allo** and **24-allo**, respectively. (B): Trace (λ_{det} = 680 nm) from the reaction after stirring overnight at 40 °C, which shows the formation of a number of putative chlorins.

Ultimately, neat TFA was used to remove the 2-(trimethylsilyl)ethyl protecting group, as described in the following early procedure.

Bacteriopheophorbide *a* (Bpheide *a*). Neat TFA was degassed by bubbling with argon for 15 min. A sample of crude **24** (4.82 mg containing 5.07 µmol of **24**) was treated with the neat degassed TFA (2.6 mL). The reaction mixture was stirred at room temperature for 15 min. The resulting solution was concentrated and chromatographed [ultra-pure grade silica, CH_2Cl_2/MeOH (20:1)] to afford a first fraction; switching to CH_2Cl_2/MeOH (5:1) afforded a second fraction.

The first fraction contained the title compound (dark brown residue, 2.32 mg, 75%) as a mixture of two epimers in 85:15 ratio. The following spectroscopic data are listed for the main epimer only: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.97 (s, 1H), 8.47 (s, 1H), 8.41 (s, 1H), 6.10 (s, 1H), 4.26–4.29 (m, 2H), 4.01–4.04 (m, 2H), 3.83 (s, 3H), 3.49 (s, 3H), 3.41 (s, 3H), 3.16 (s, 3H), 2.54–2.56 (m, 2H), 2.29–2.37 (m, 2H), 2.19–2.32 (m, 1H), 2.03–2.09 (m, 1H), 1.78 (d, J = 7.5 Hz, 3H), 1.72 (d, J = 7.5 Hz, 3H), 1.10 (t, J = 7.3 Hz, 3H), 0.47 (brs, 1H), –0.96 (brs, 1H); ^{13}C{^{1}H} NMR

($CDCl_3$, 175 MHz) δ 199.30, 189.19, 176.92, 171.23, 169.79, 169.69, 163.81, 158.10, 148.26, 139.22, 138.49, 137.00, 136.48, 133.43, 128.73, 121.49, 108.12, 99.78, 97.82, 95.99, 64.51, 55.09, 53.00, 50.70, 49.89, 49.02, 33.49, 30.32, 29.51, 23.04, 22.84 ,13.58, 11.67, 10.91; several expected ^{13}C resonance in the aliphatic region was not found.

The second fraction (dark brown residue, 1.98 mg) contained components in addition to tetrapyrrole macrocycles whereupon structural elucidation was not possible by ^1H NMR spectroscopy. RP-HPLC analysis (with λ_{det} = 254 and 752 nm), however, gave data consistent with the allomerization product (t_R = 7.51 min) as 13^2-hydroxybacteriopheophorbide *a*. The crude product here corresponds to fraction *4* in Fig. S14. The data for the crude product are shown in Fig. S16. HPLC-MS data *m/z* = 626.40 (positive mode) and *m/z* = 625.30 (negative ion mode). Data of the isolated sample are as follows. MALDI-MS data: *m/z* = 626.152 $[M^-]^+$ with use of CHCA as a matrix. Data in diethyl ether: λ_{abs} (nm) 356, 385, 522, 752; I_{Qy}/I_B = 0.53; λ_{em} (nm) 761. Data in CH_2Cl_2: λ_{abs} (nm) 360, 390, 526, 759; I_{Qy}/I_B = 0.48; λ_{em} (nm) 771.

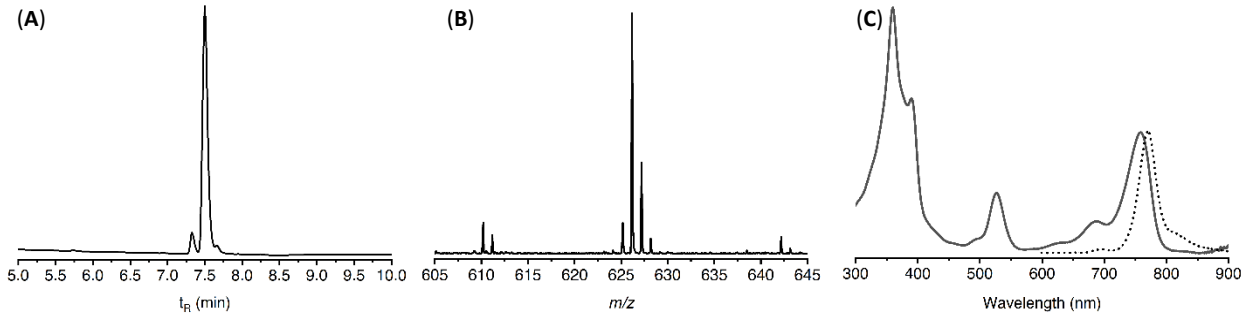


Fig. S16. Analysis of the second fraction: (A) RP-HPLC profile (λ_{det} 745 nm) showing two epimers (t_R = 7.33 and 7.51 min) (see Experimental Section for conditions). (B) MALDI-MS spectrum. (C) Absorption (solid line) and emission (dotted line) spectra in CH_2Cl_2 at room temperature.

X. Macrocycle characterization data

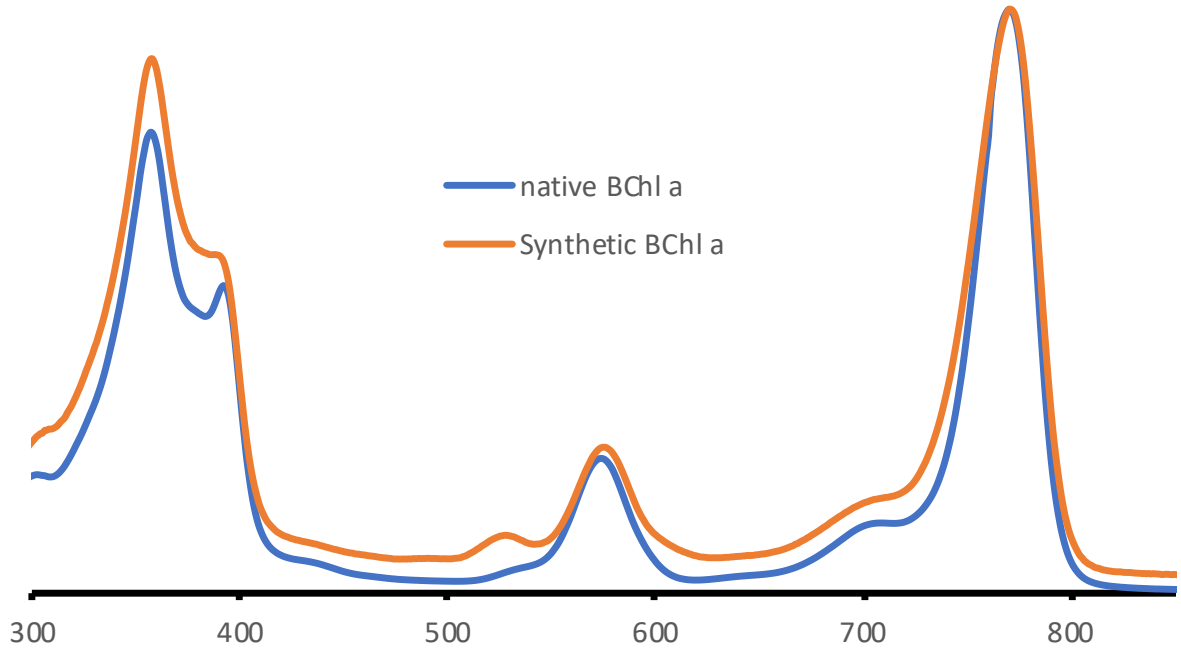


Fig. S17. Absorption spectra of synthetic and native **BChl *a*** in diethyl ether at room temperature.

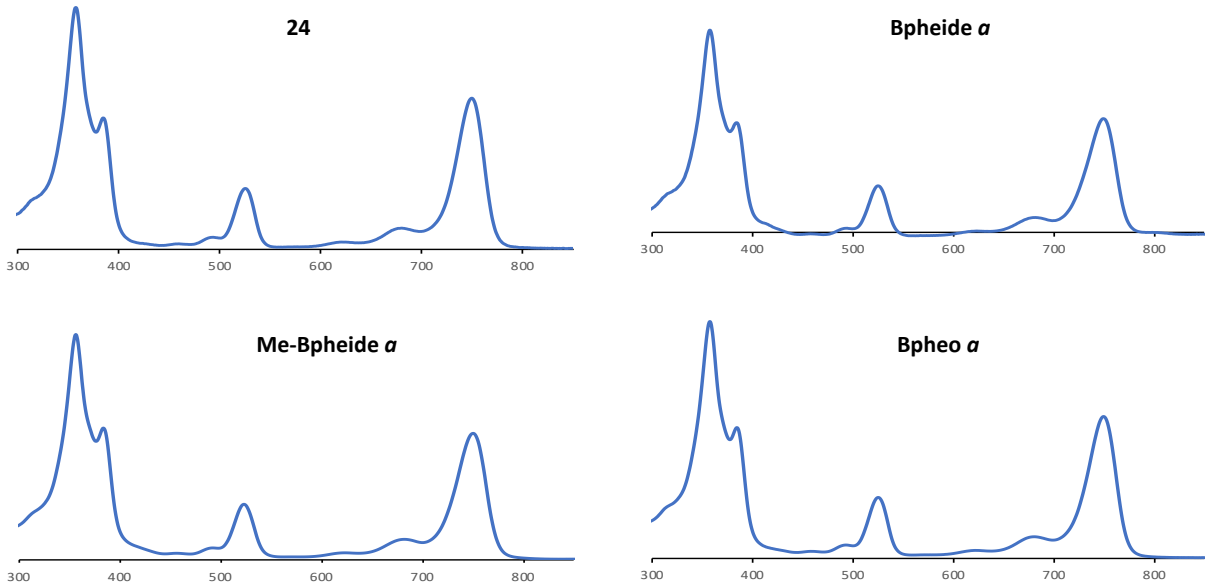


Fig. S18. Absorption spectra of synthetic free base macrocycles in diethyl ether at room temperature.

Table S4 Absorption spectral features of synthetic versus native-origin macrocycles

Compound	solvent	λ_{abs} (B), nm	λ_{abs} (Q_x), nm	λ_{abs} (Q_y), nm	I_{Qy}/I_B	Source
24	Et_2O	357, 384	525	749	0.62	here
Bpheide *a*	Et_2O	357, 384	525	749	0.56	here
Lit: Bpheide *a*	Et_2O	356, 382	524	749	0.62	Ref. 85
Me Bpheide *a*	Et_2O	357, 384	523	750	0.56	here
Lit: Me Bpheide *a*	CH_2Cl_2	360, 387	528	753	0.52	Ref. 83
Lit: Me Bpheide *a*	pyridine	354, 383	524	746	0.65	Ref. 84
Bpheo *a*	Et_2O	357, 384	524	749	0.63	here
Lit: Native Bpheo *a*	Et_2O	356, 388	524	749	0.61	Ref. 85
BChl *a*	Et_2O	357, 388	575	770	1.09	here
Lit: Native BChl *a*	Et_2O	356, 391	573	769	1.21	Ref. 85

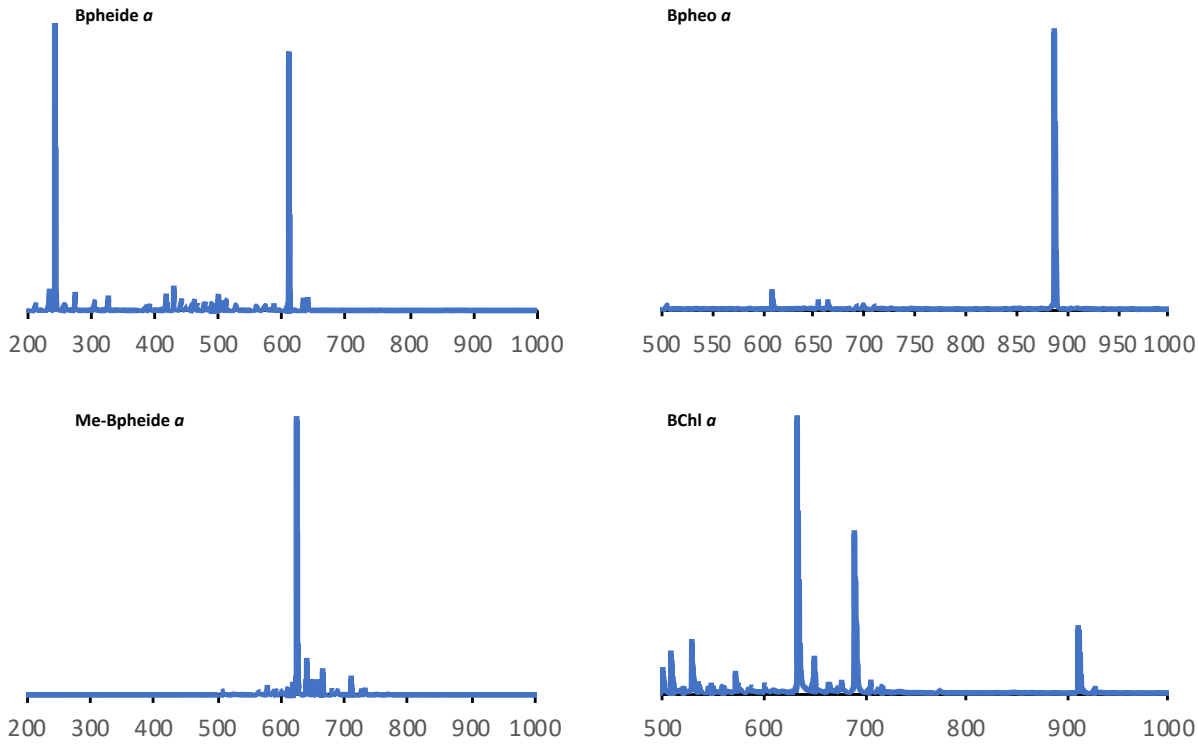


Fig. S19. MALDI-MS spectra of synthetic macrocycles (peak intensity versus *m/z*). See the Experimental Section for matrices.

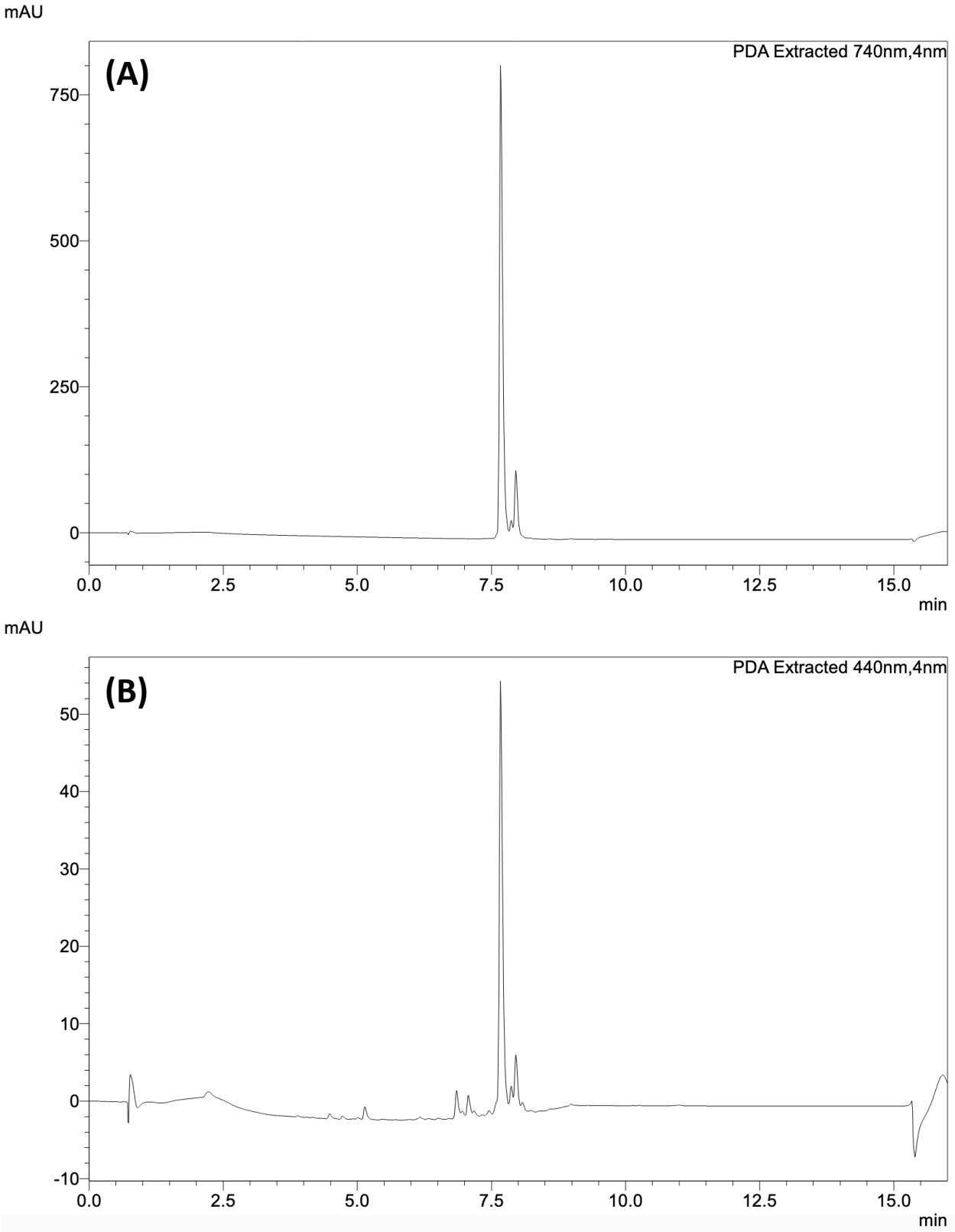


Fig. S20. RP-HPLC chromatograms of **Bpheide *a*** at λ_{det} = 740 nm (panel A) and at λ_{det} = 440 nm (panel B). An excerpt of the former is shown in Fig. 6 panel D. (see Experimental Section for conditions).

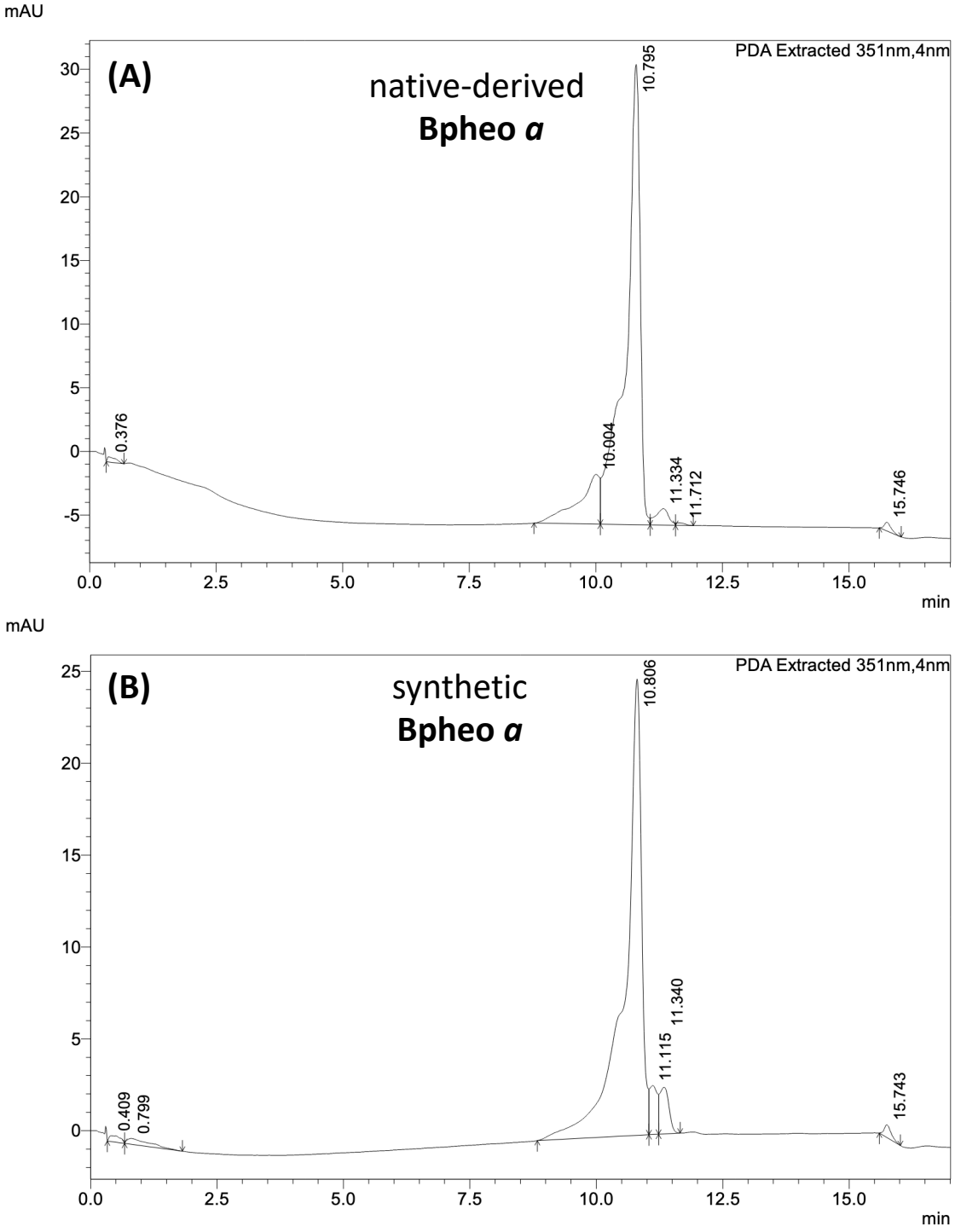


Fig. S21. RP-HPLC chromatograms of **Bpheo *a*** with λ_{det} = 351 nm. (A) Synthetic **Bpheo *a***. (B) Native-derived **Bpheo *a***. Analysis was carried out via reversed-phase (non-chiral) HPLC using a Shim-pack XR-ODS column (2.2 μm, 3.0 x 50 mm), a column temperature of 40 °C, a flowrate of 0.5 mL/min, injection volume of 0.3 μL (sample dissolved in a 1:1 ratio of CH_2Cl_2:acetonitrile); the void volume was ~0.8 minutes. The solvents A (water with 0.1% formic acid) and B (acetonitrile with 0.1% formic acid) were used in a gradient: 3 min (90% of B), 7 min (90% of B to 95% of B), 5 min (95% of B) and 2 min (5% of B).

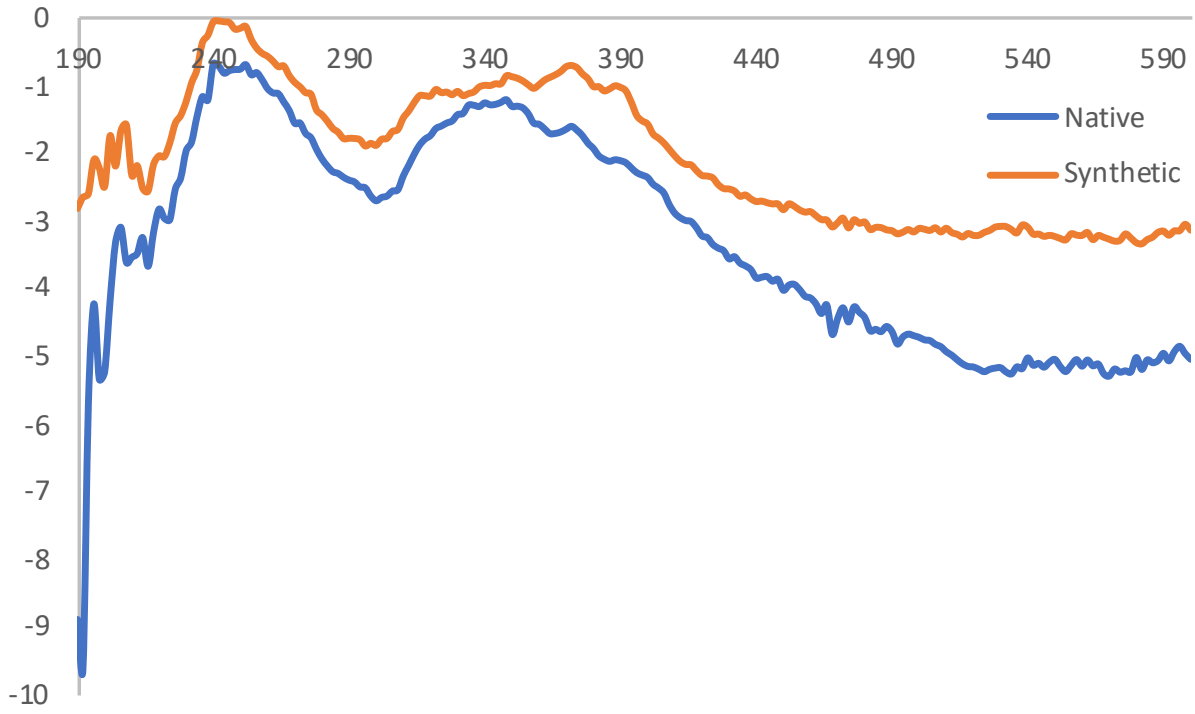
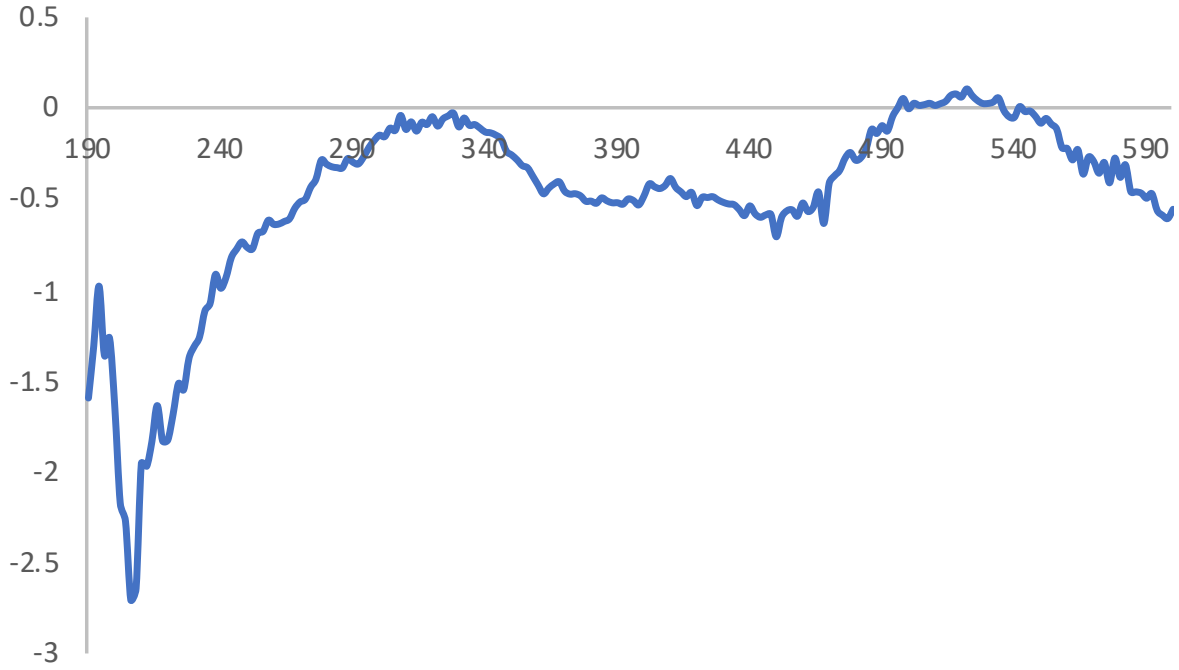


Fig. S22. CD spectra (mdeg) of synthetic and native **Bpheo *a*** in acetonitrile at room temperature (c = 10^{-5} M, average from 16 scans, background subtraction, cuvette length: 1 mm) using an Applied Photophysics π*−180 instrument.



Background for spectra in Fig. 22. CD spectra of acetonitrile at room temperature (average from 16 scans, background subtraction, cuvette length: 1 mm, instrument: Applied Photophysics π*−180).

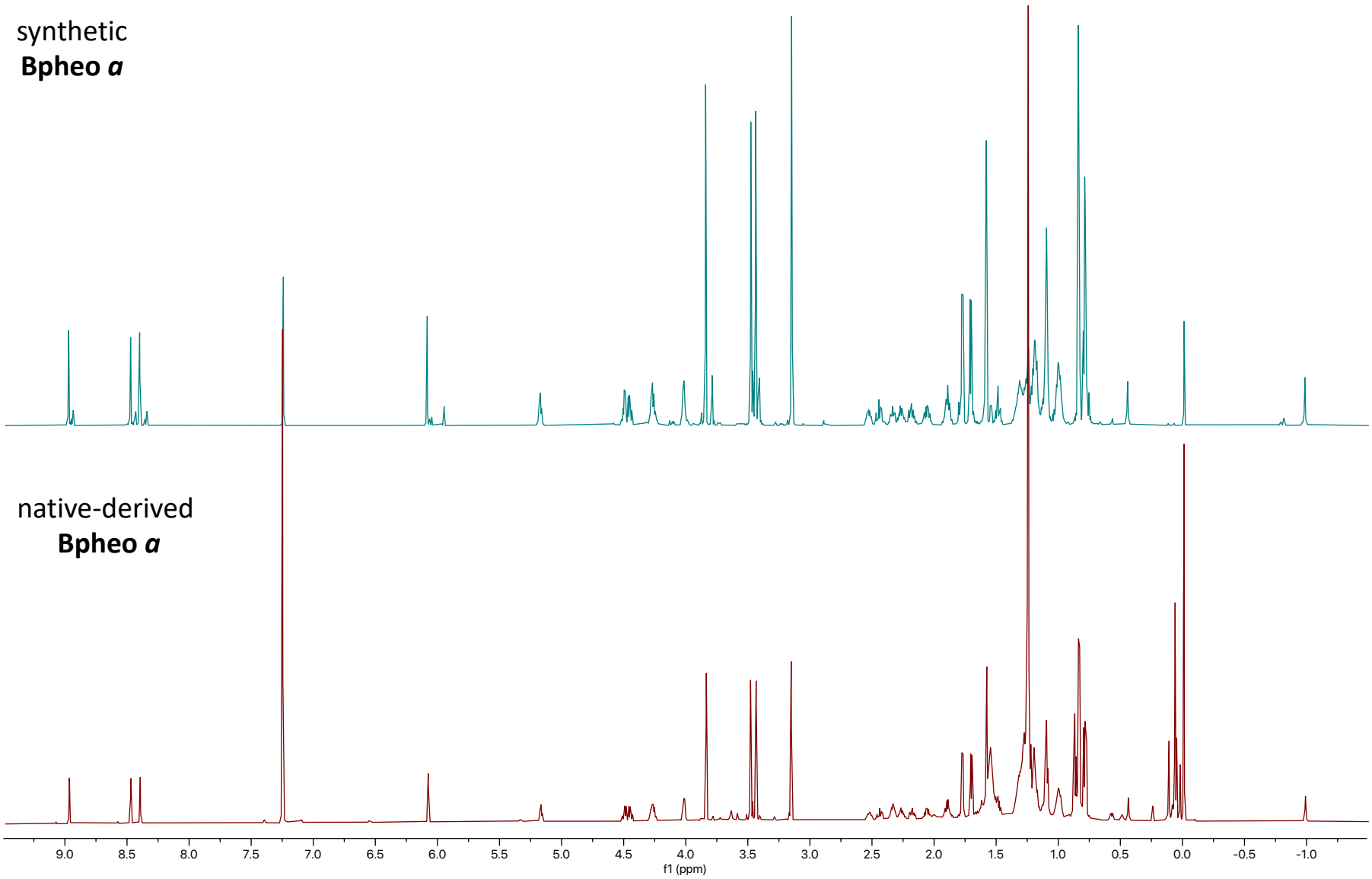


Fig. S23. ^{1}H NMR spectra of synthetic **Bpheo *a*** and native-derived **Bpheo *a*** at room temperature in $CDCl_3$ (Bruker Avance NEO 700 MHz).

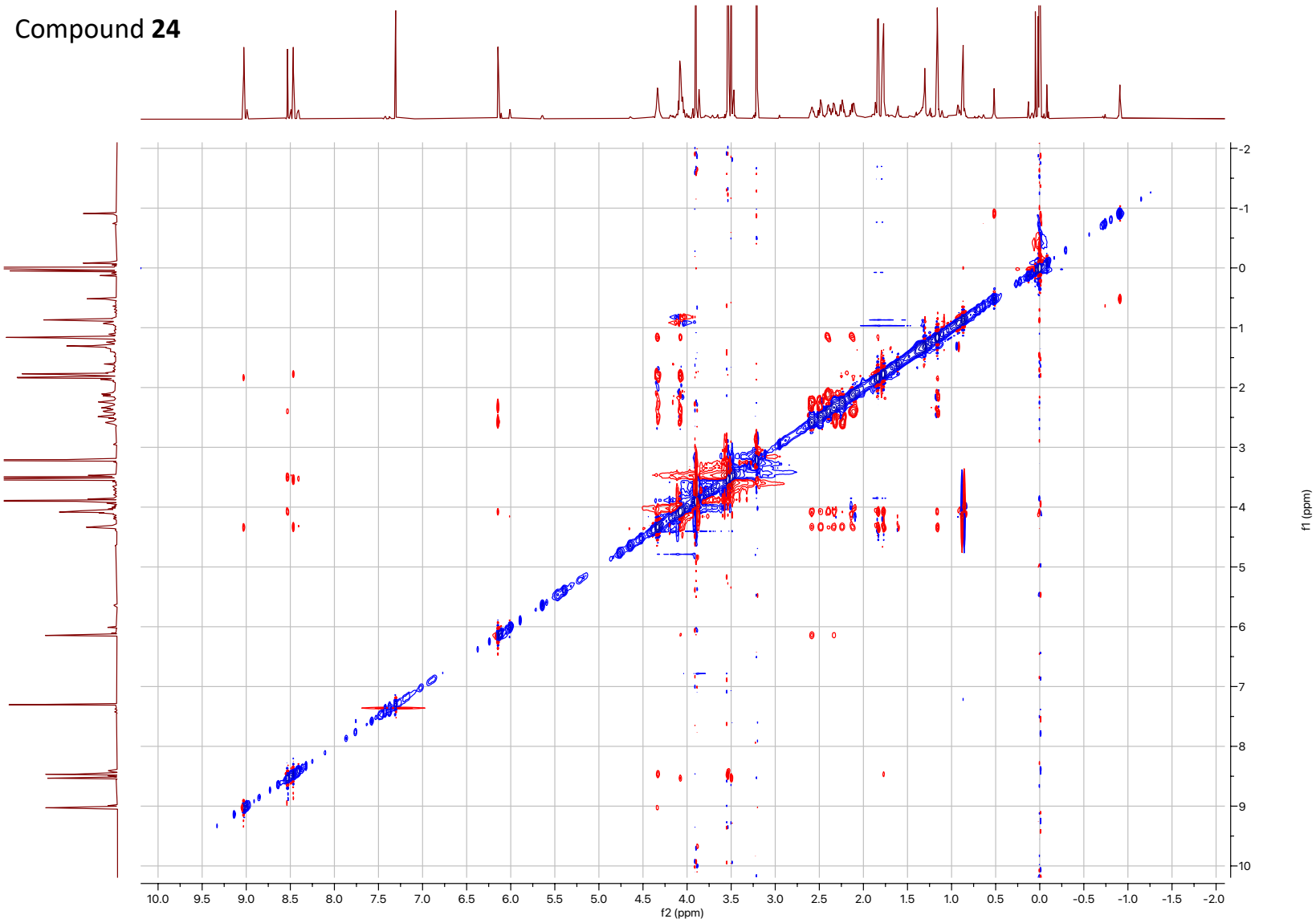


Fig. S24a. ROESY analysis for **24** in $CDCl_3$ at room temperature.

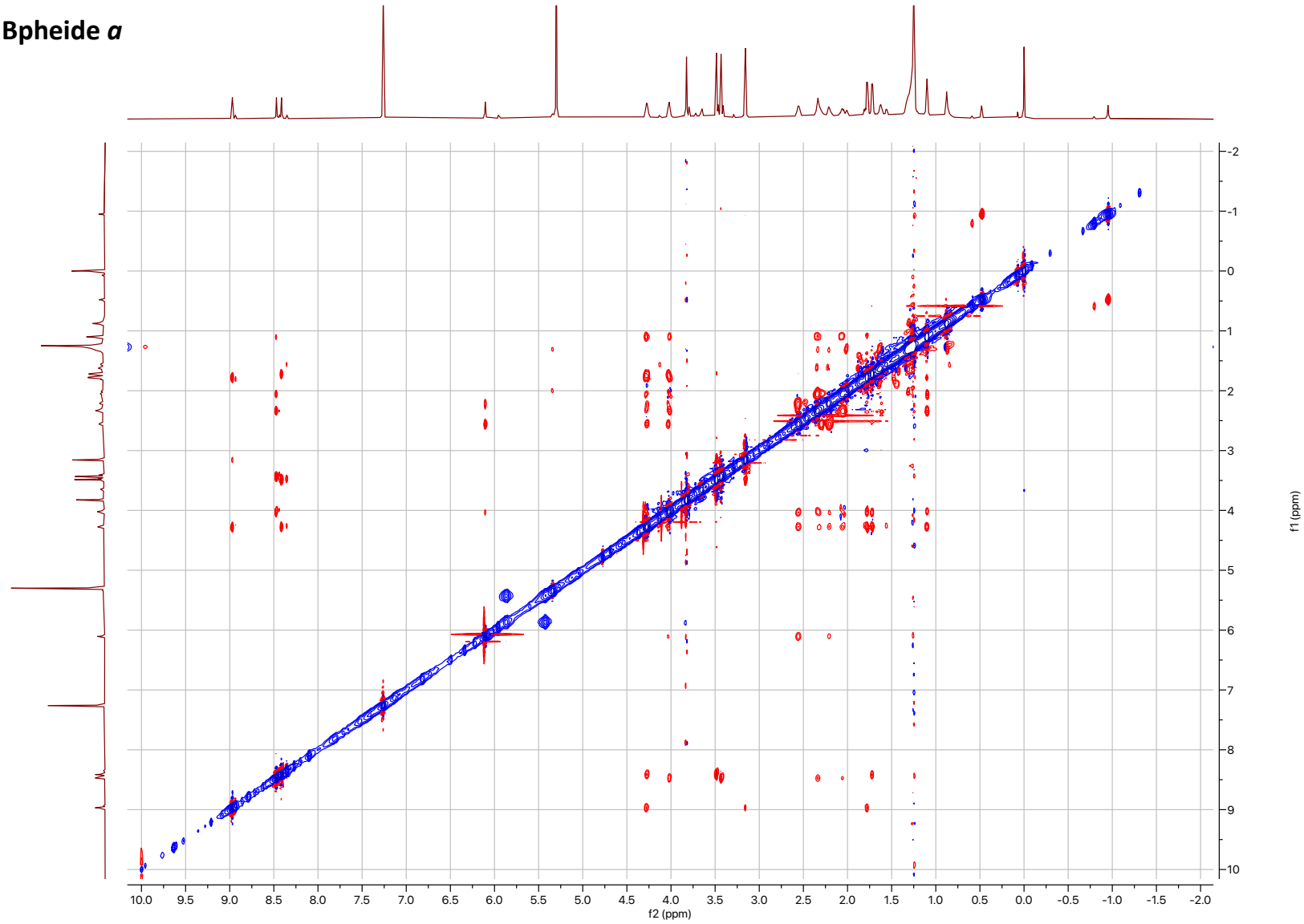


Fig. S24b. ROESY analysis for **Bpheide *a*** in $CDCl_3$ at room temperature.

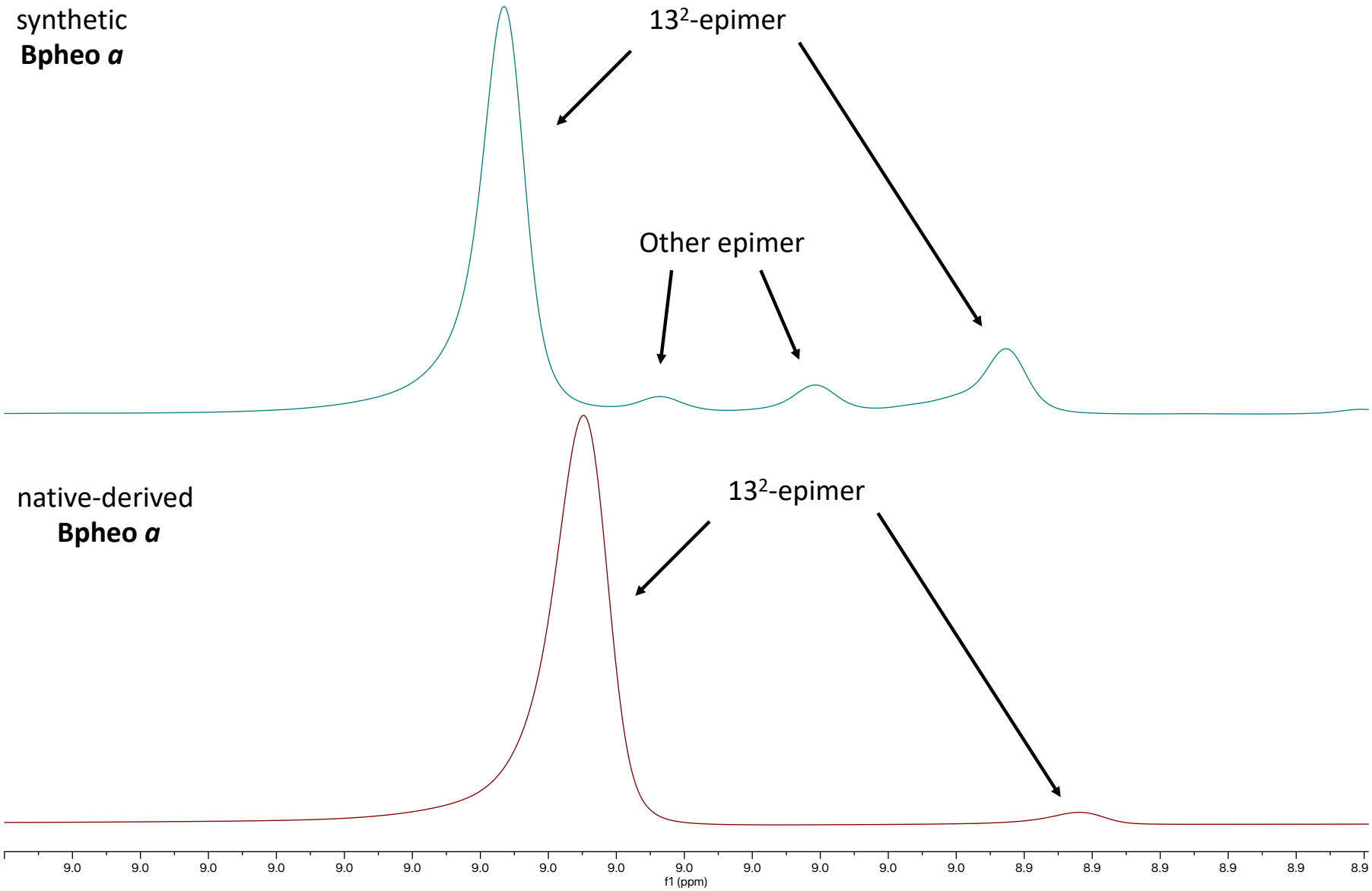


Fig. S25. ^{1}H NMR spectra of synthetic **Bpheo *a*** and native-derived **Bpheo *a*** showing the region assigned to the H^{5} resonance.

XI. Molar absorption coefficient determinations

Compound 22:

A sample of 3.85 mg of compound **22** was placed in a 5 mL volumetric flask and dissolved in acetonitrile (HPLC grade). The solution was diluted to the mark to obtain the stock solution. An aliquot of 0.5 mL of this stock solution was then transferred using a 1 mL microsyringe and further diluted to 10 mL using a 10-mL volumetric flask with acetonitrile to prepare the final solution. The absorption measurement was done in a 1-cm pathlength quartz cuvette, whereupon the maximum was A = 1.55 (at λ = 242 nm).

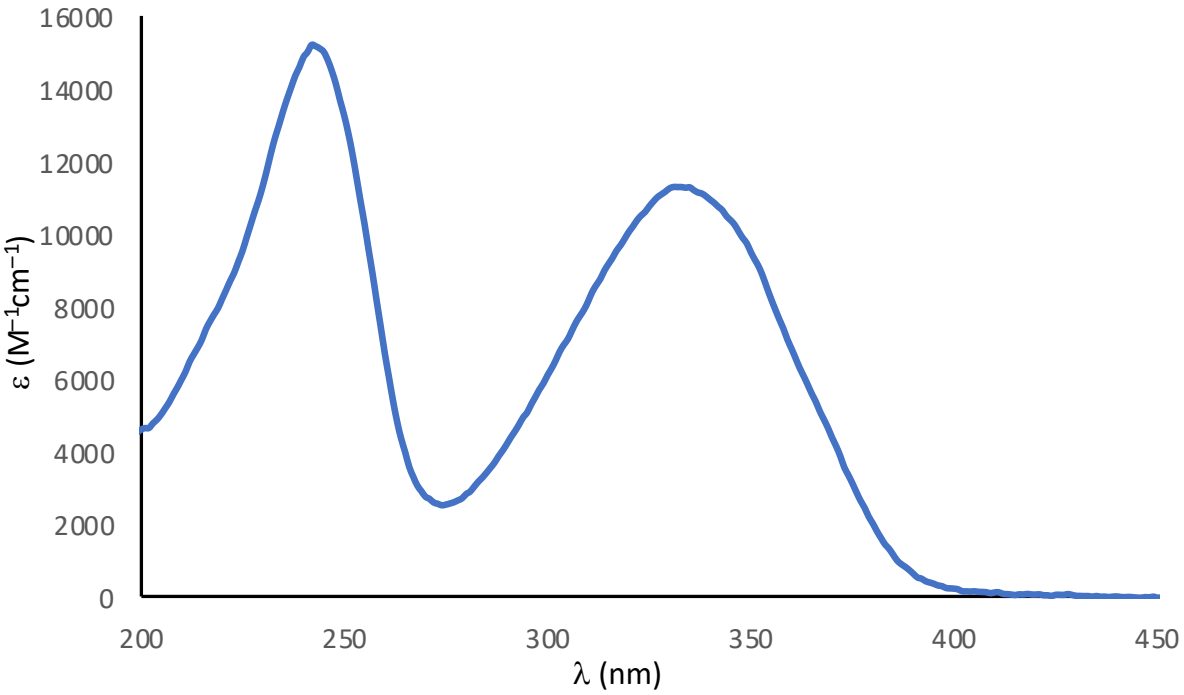


Fig. S26. Absorption spectrum in acetonitrile at room temperature of **22**.

Compound 23:

A sample of 4.49 mg of compound **23** was placed in a 5 mL volumetric flask and dissolved in acetonitrile (HPLC grade). The solution was diluted to the mark to obtain the stock solution. An aliquot of 0.5 mL of this stock solution was then transferred using a 1 mL microsyringe and further diluted to 10 mL using a 10-mL volumetric flask with acetonitrile to prepare the final solution. The absorption measurement was done in a 1-cm pathlength quartz cuvette, whereupon the maximum was A = 1.77 (at λ = 240 nm).

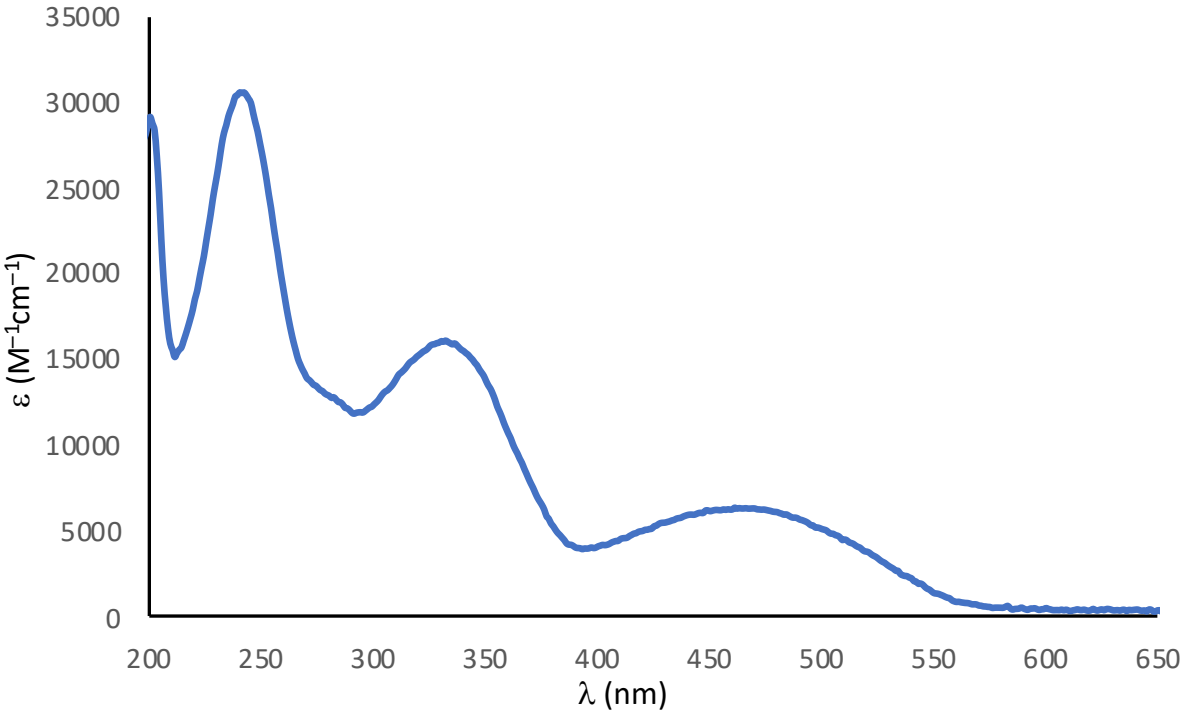


Fig. S27. Absorption spectrum in acetonitrile at room temperature of **23**.

Compound 24:

A sample of 3.74 mg of compound **24** was dissolved in 2 mL of CH_2Cl_2 (HPLC grade). An aliquot of 0.1 mL of this stock solution was then transferred using a 1 mL microsyringe and further diluted to 10 mL using a 10-mL volumetric flask with CH_2Cl_2 to prepare the final solution. The absorption measurement was done in a 1-cm pathlength quartz cuvette, whereupon the maximum was A = 2.13 (at λ = 360 nm).

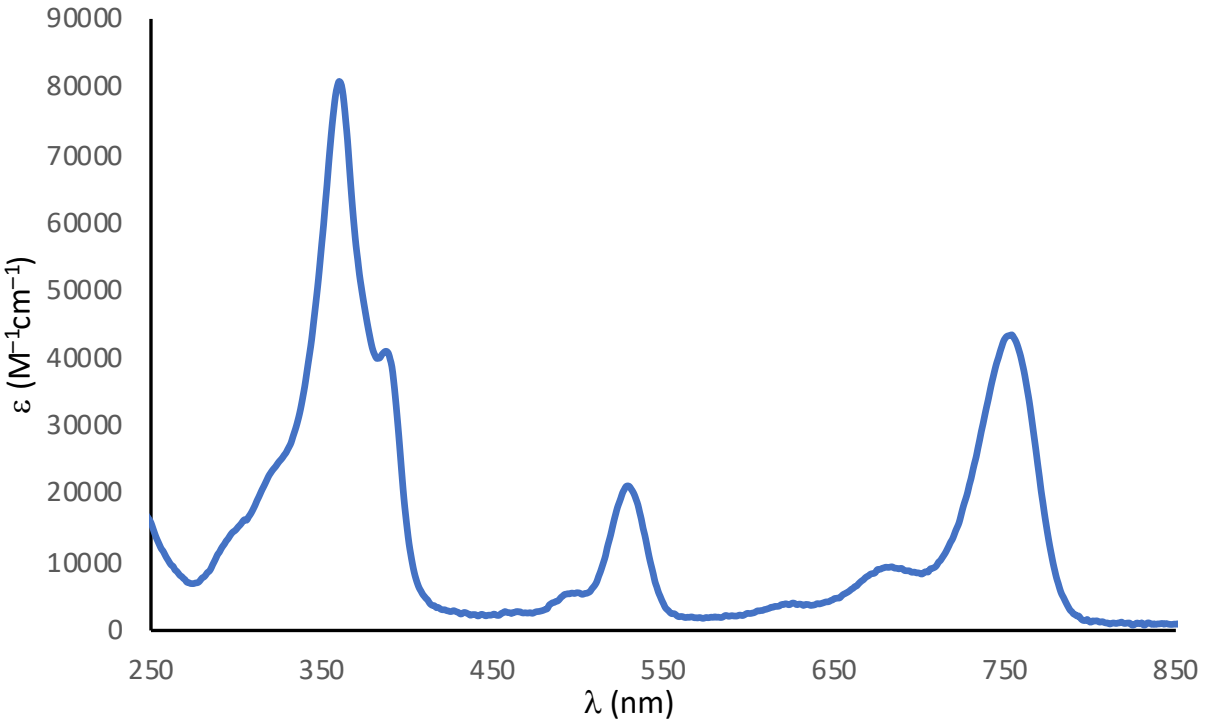
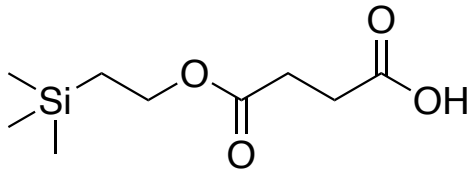


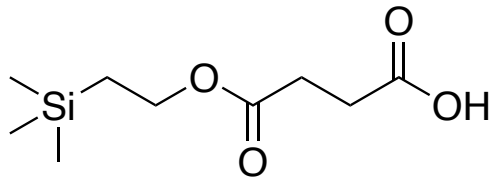
Fig. S28. Absorption spectrum in CH_2Cl_2 at room temperature of **24**.

XII. Spectral data

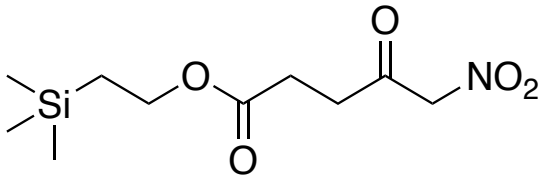
^{1}H NMR (500 MHz, $CDCl_3$)



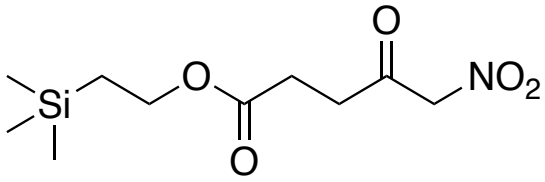
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



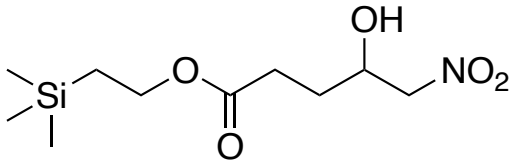
^{1}H NMR (500 MHz, $CDCl_3$)



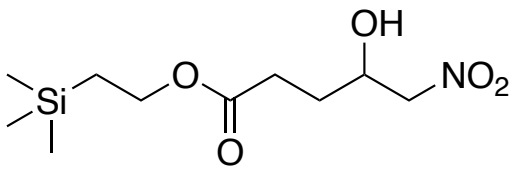
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



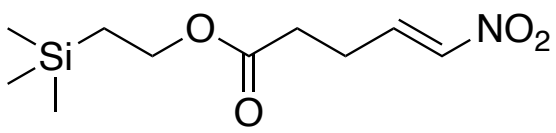
^{1}H NMR (500 MHz, $CDCl_3$)



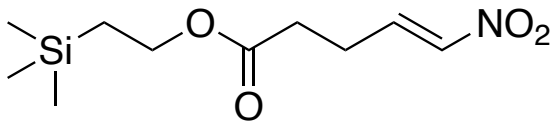
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



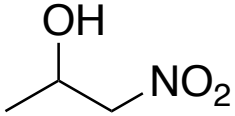
^{1}H NMR (500 MHz, $CDCl_3$)



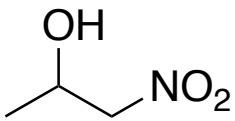
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



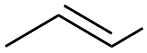
^{1}H NMR (500 MHz, $CDCl_3$)



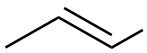
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

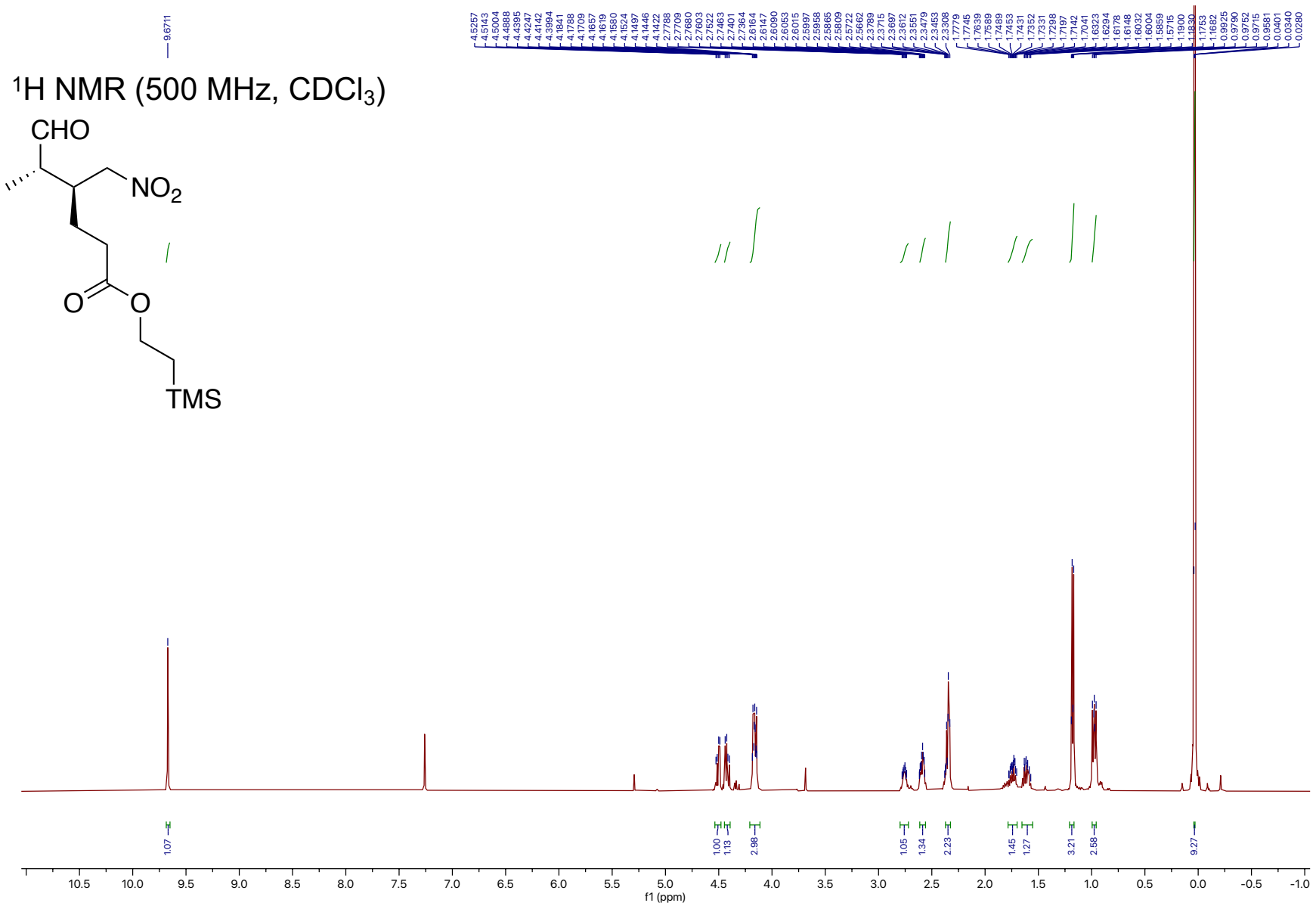


^{1}H NMR (500 MHz, $CDCl_3$)

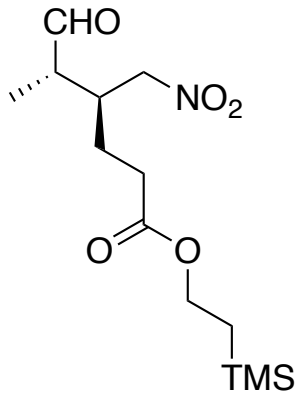


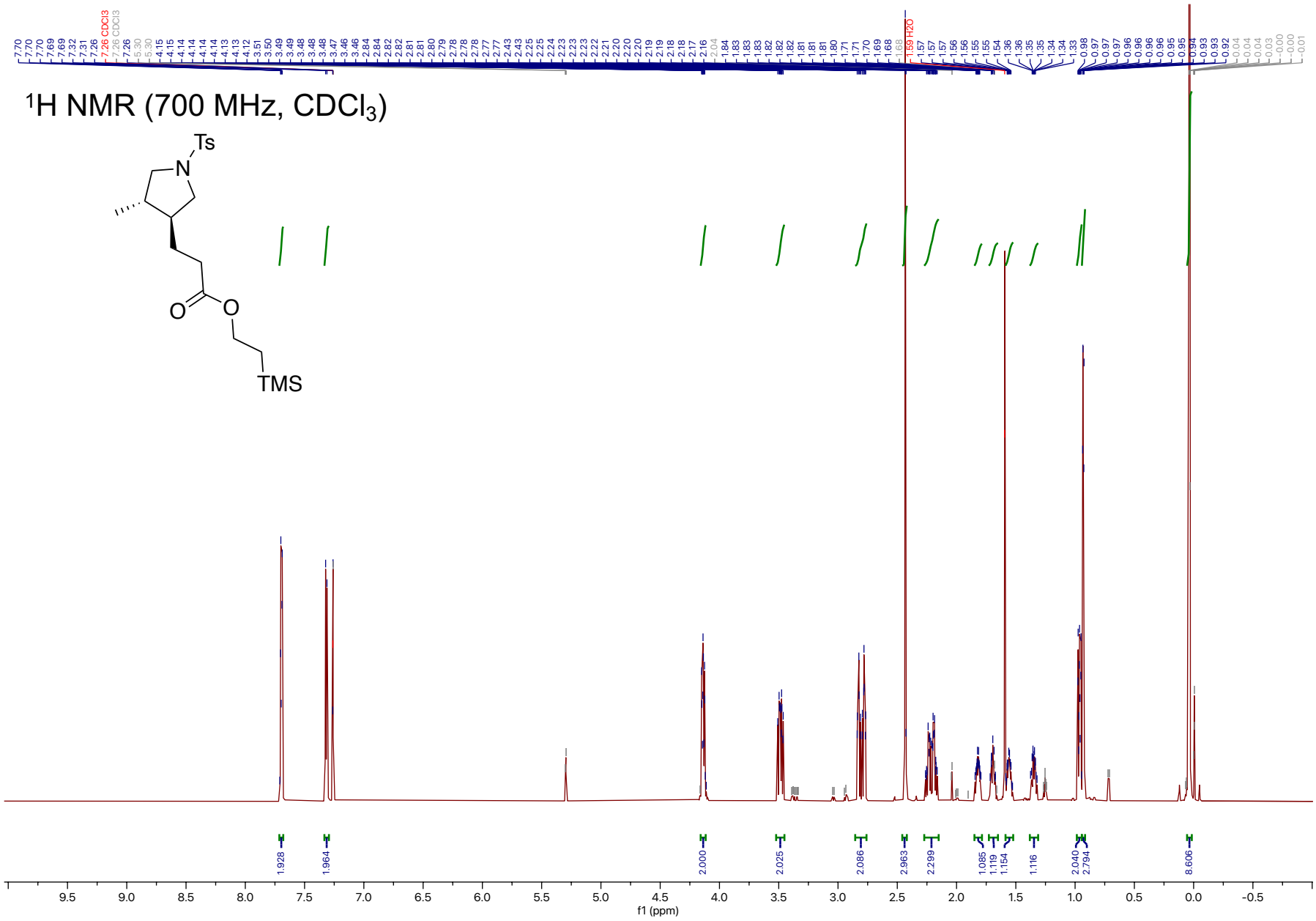
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

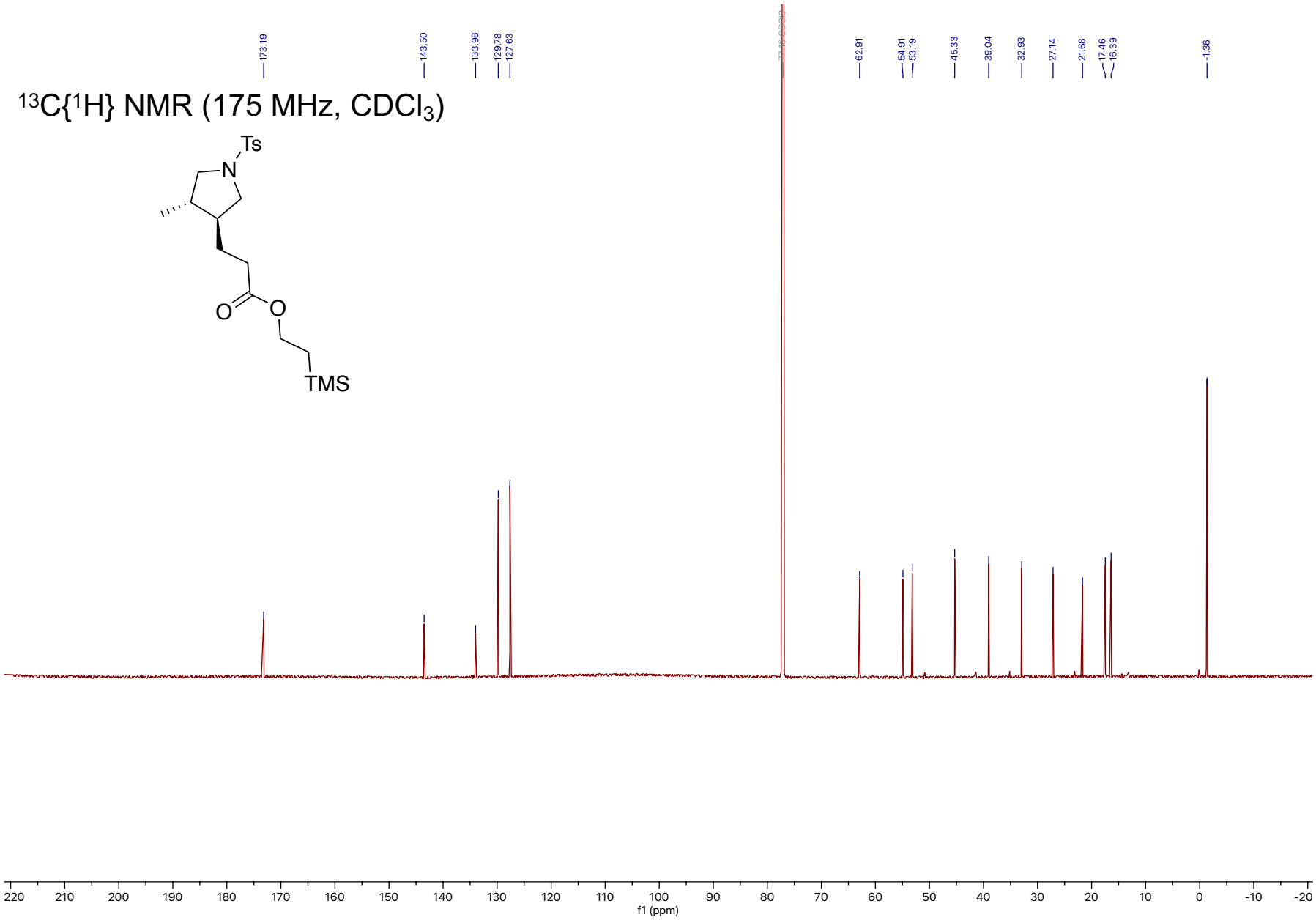



^{1}H NMR (500 MHz, $CDCl_3$)
CHO
NO_2
O
O
TMS
f1 (ppm)

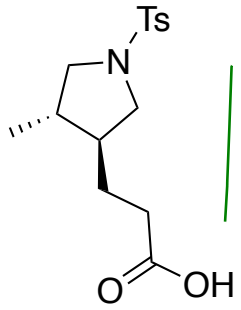
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



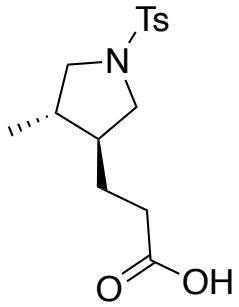

1H NMR (700 MHz, CDCl3)
Ts
N
O
O
TMS
f1 (ppm)

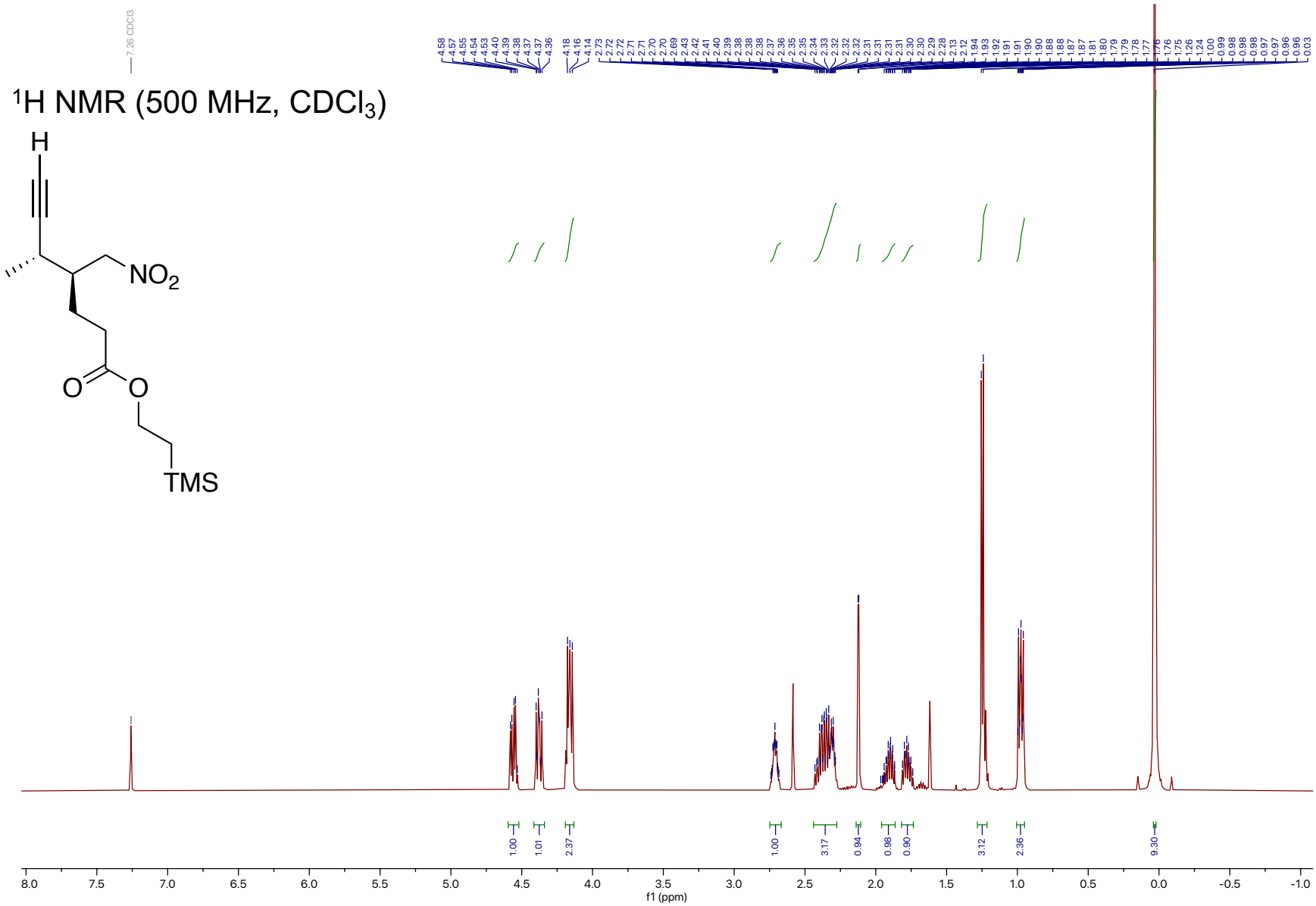

$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$)
Ts
N
O
O
TMS
173.19
143.50
133.98
129.78
127.63
77.48
62.91
54.91
53.19
45.33
39.04
32.93
27.14
21.68
17.46
16.39
-1.36
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$)

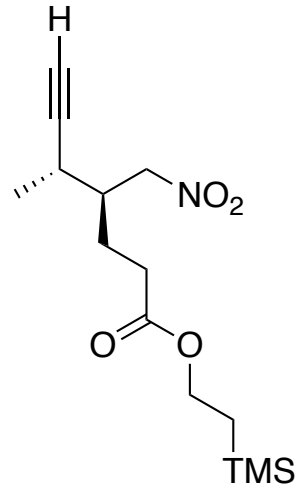


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)

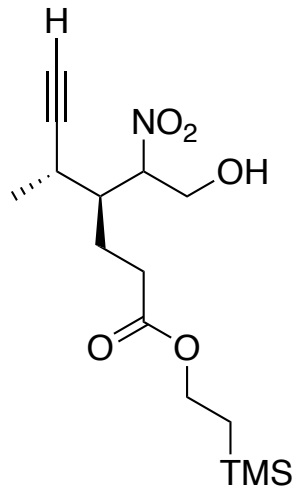



^{1}H NMR (500 MHz, $CDCl_3$)
H
NO_2
O
O
TMS
7.26 CDCl3
f1 (ppm)

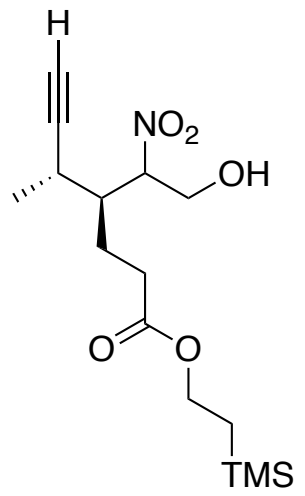
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$)



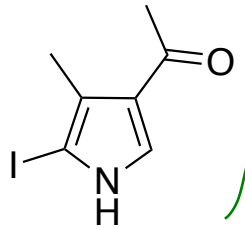
^{1}H NMR (500 MHz, $CDCl_3$)

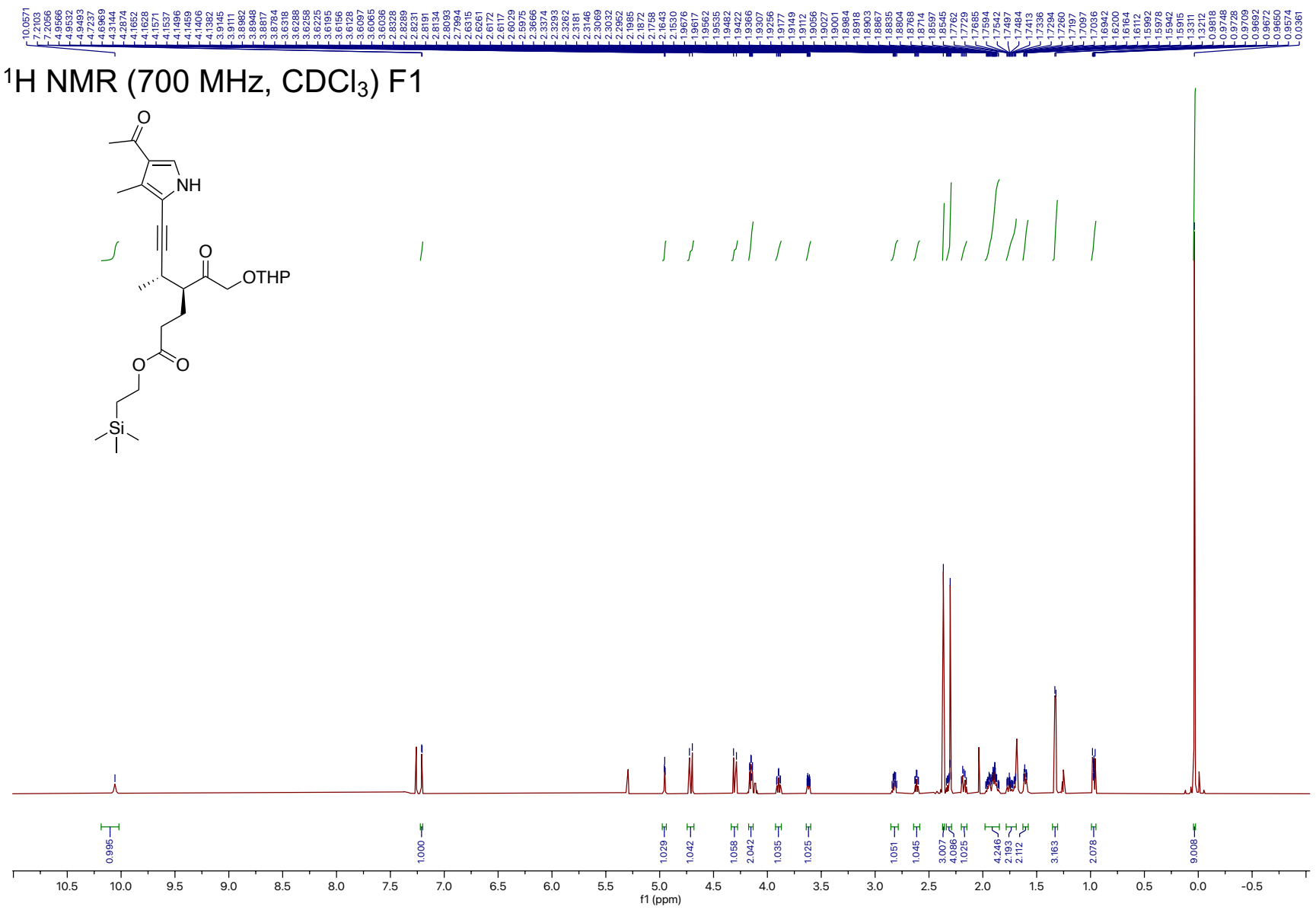


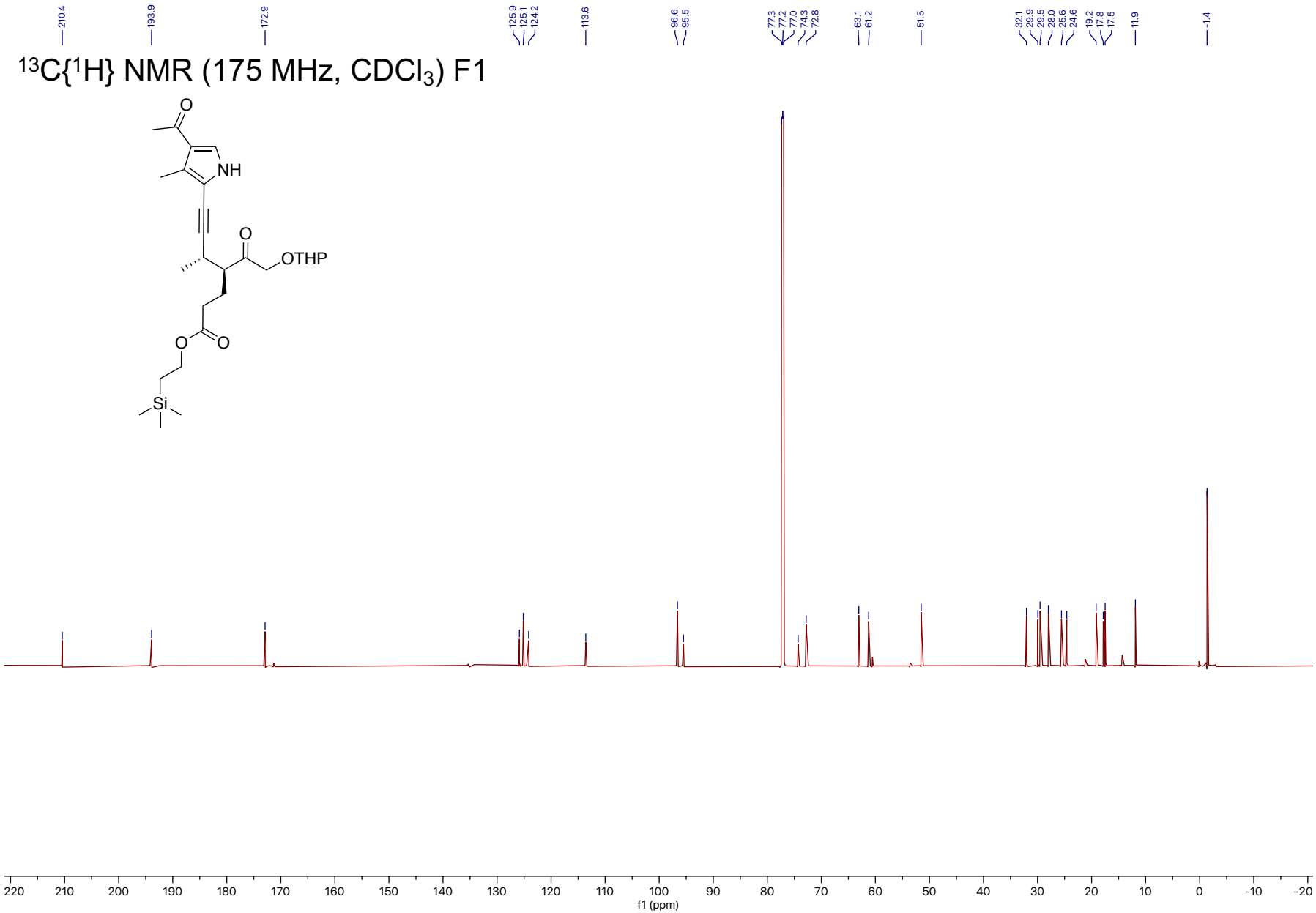
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



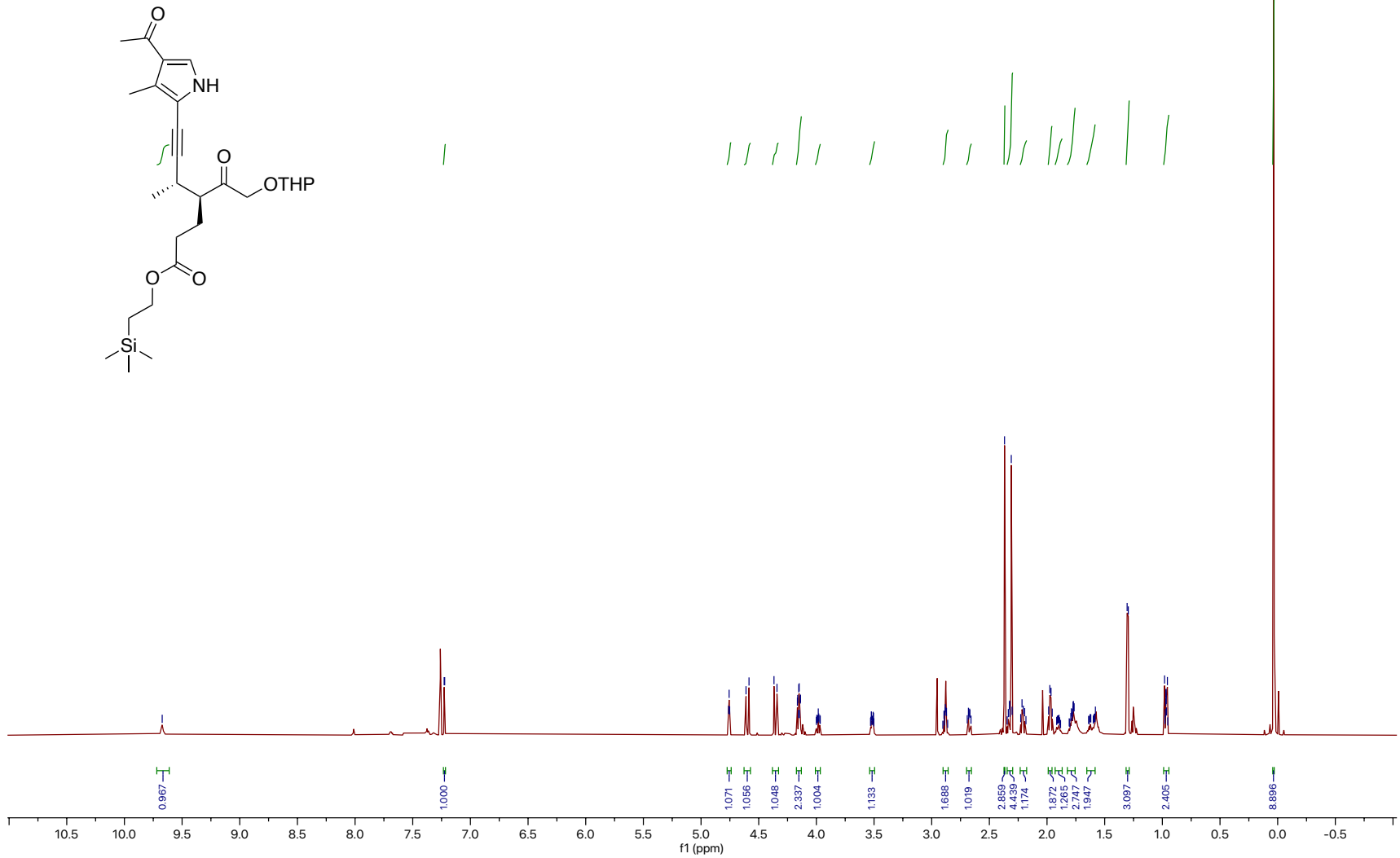
^{1}H NMR (500 MHz, $CDCl_3$)

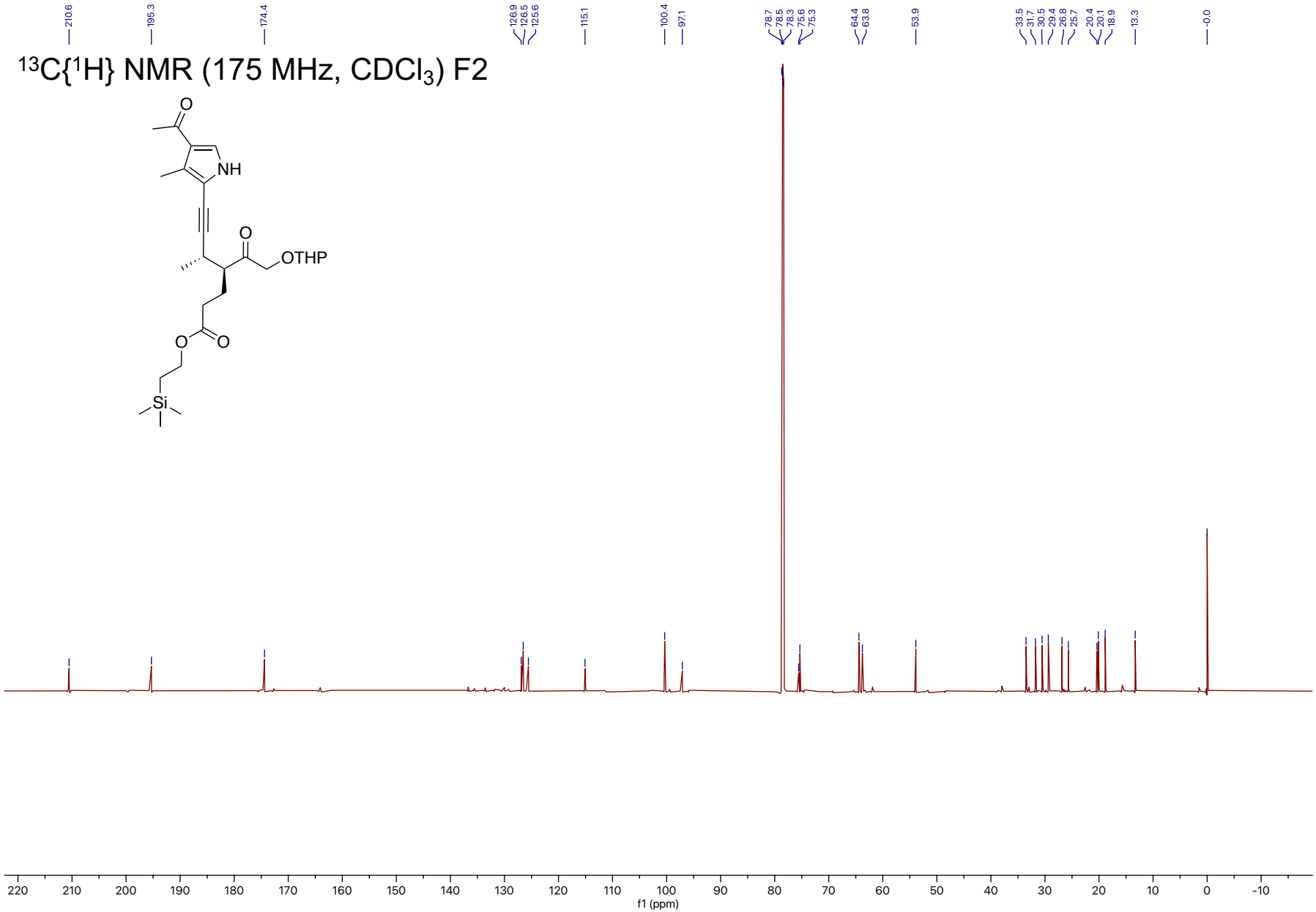



^{1}H NMR (700 MHz, $CDCl_3$) F1
O
NH
O
OTHP
O
O
Si
f1 (ppm)

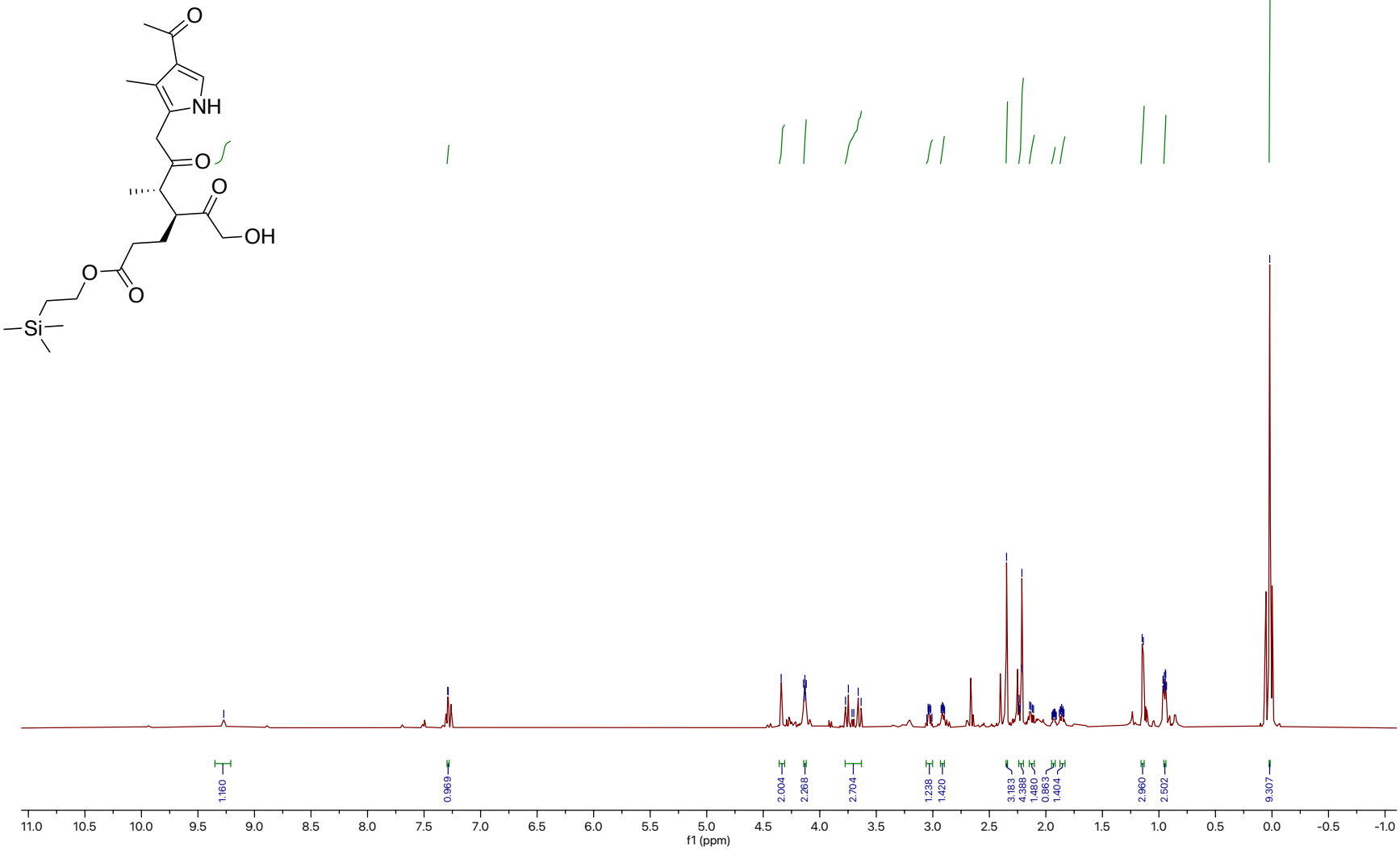

210.4
193.9
172.9
125.9
125.1
124.2
113.6
96.6
95.5
77.3
77.2
77.0
74.3
72.8
63.1
61.2
51.5
32.1
29.9
29.5
28.0
25.6
24.6
19.2
17.8
17.5
11.9
-1.4
13C{1H} NMR (175 MHz, CDCl3) F1
O
NH
O
OTHP
O
O
Si
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

^{1}H NMR (700 MHz, $CDCl_3$) F2

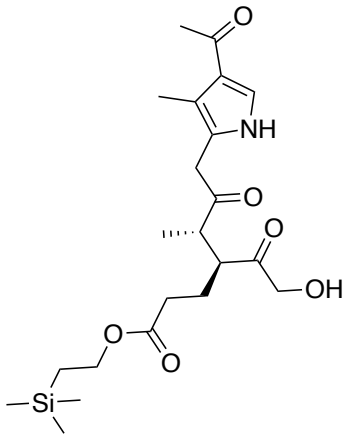


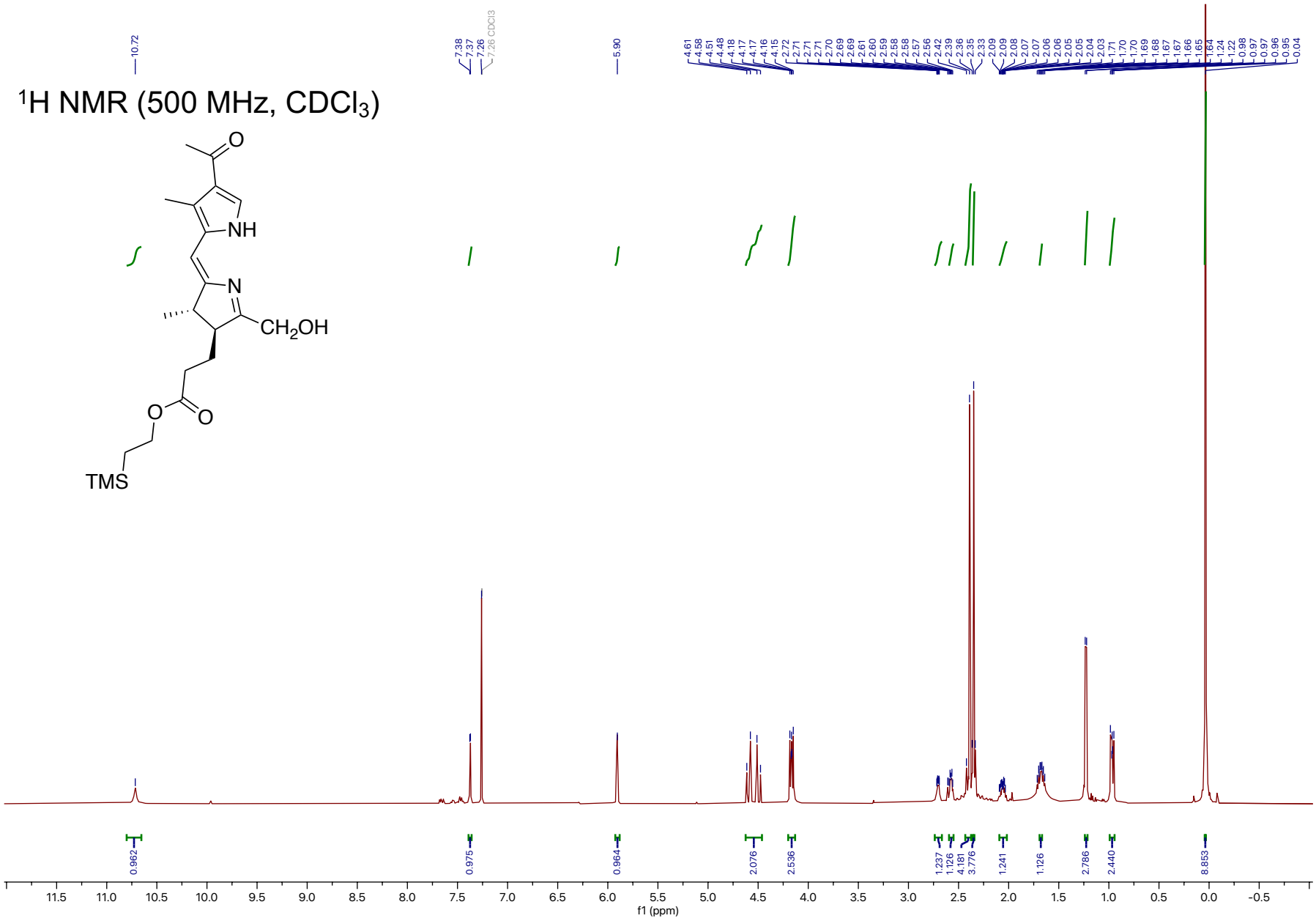

210.6
195.3
174.4
126.9
126.5
125.6
115.1
100.4
97.1
78.7
78.5
78.3
75.6
75.3
64.4
63.8
53.9
33.5
31.7
30.5
29.4
28.8
25.7
20.4
20.1
18.9
13.3
-0.0
13C{1H} NMR (175 MHz, CDCl3) F2
O
NH
O
OTHP
O
O
Si
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

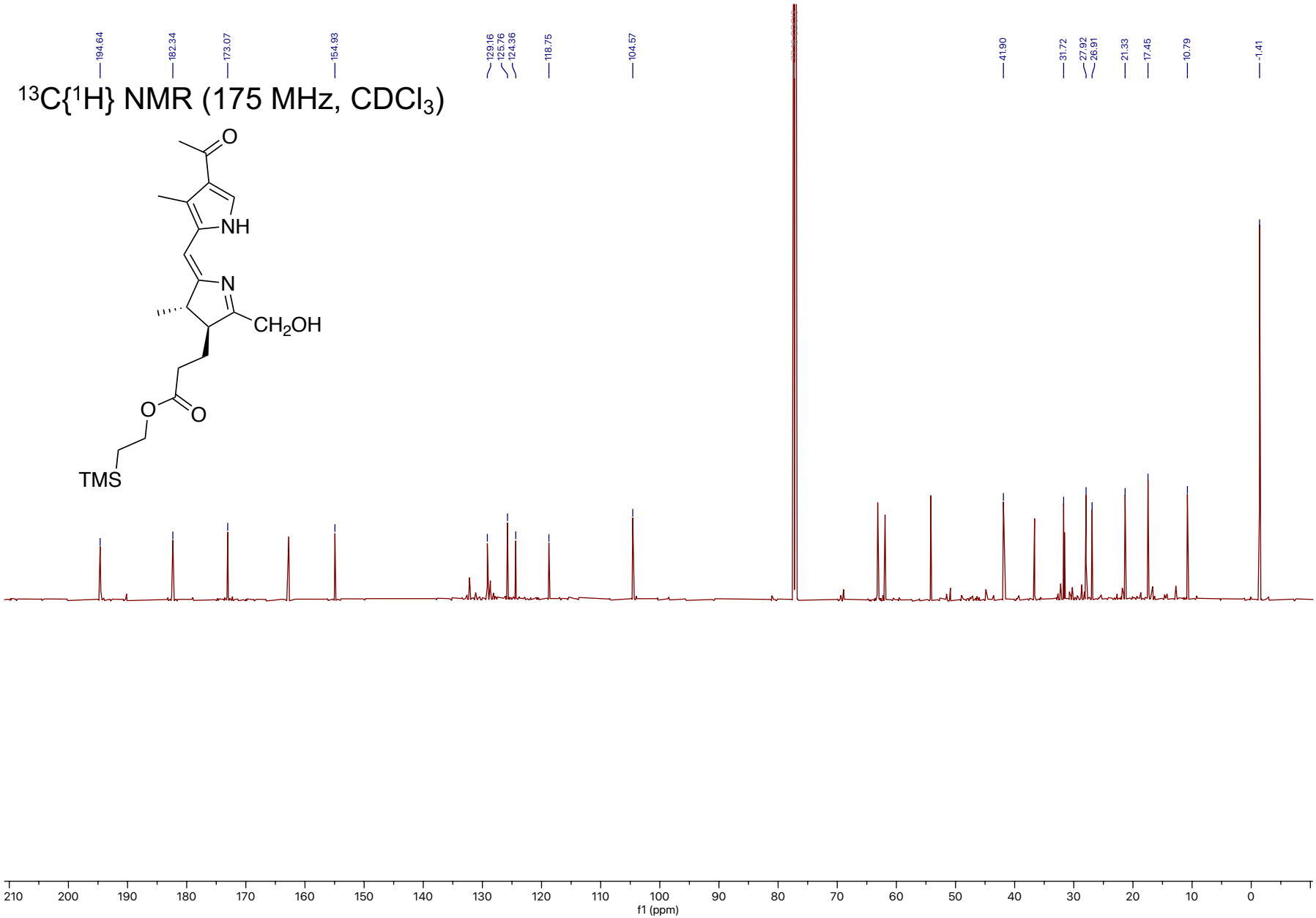
^{1}H NMR (700 MHz, $CDCl_3$)

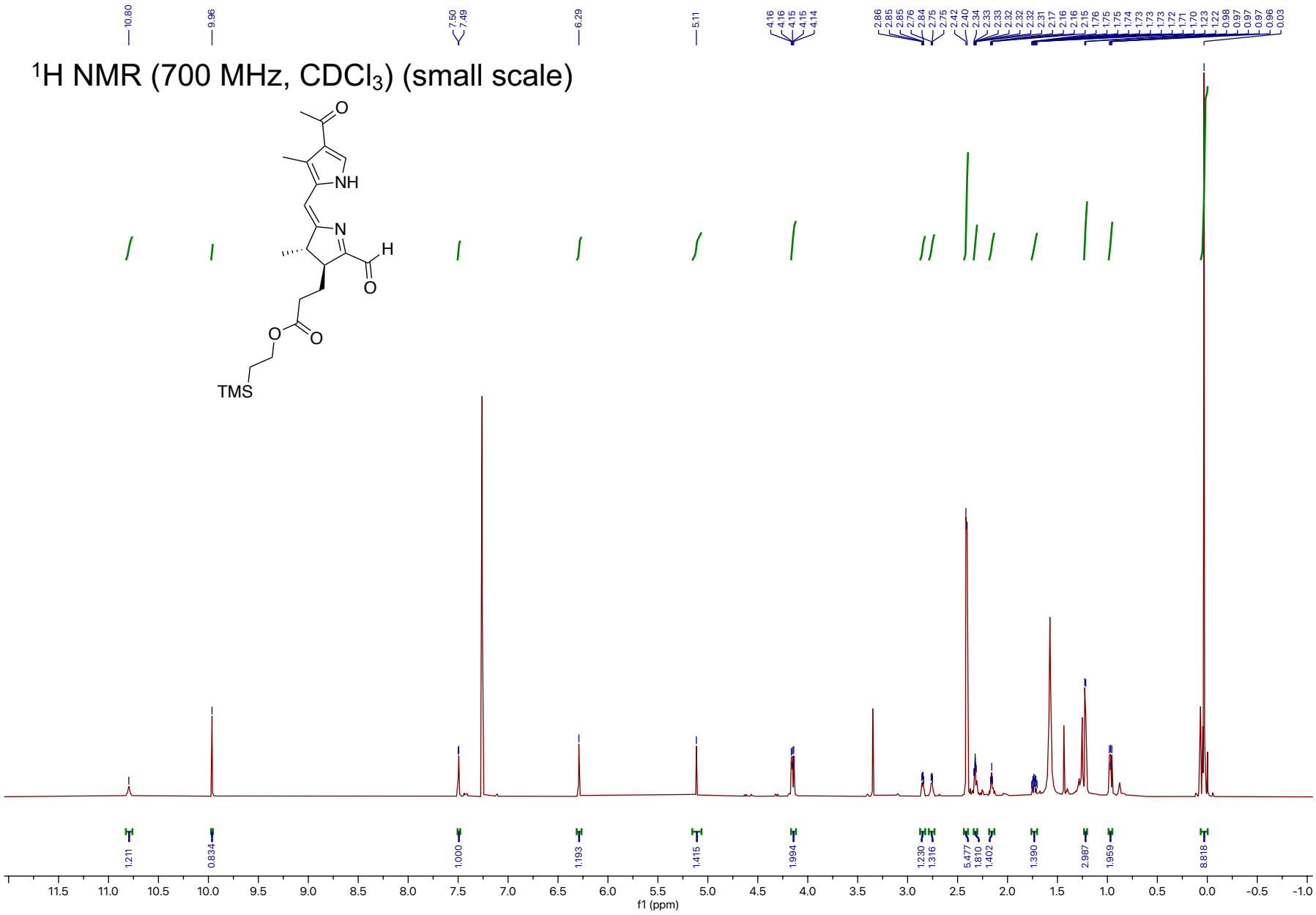


$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$)

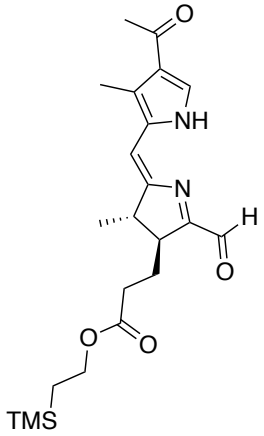



^{1}H NMR (500 MHz, $CDCl_3$)
O
NH
N
CH_2OH
O
O
TMS
10.72
7.38
7.37
7.26
7.26 CDCl3
5.90
0.962
0.975
0.964
2.076
2.536
1.237
1.126
4.181
3.776
1.241
1.126
2.786
2.440
8.853
f1 (ppm)

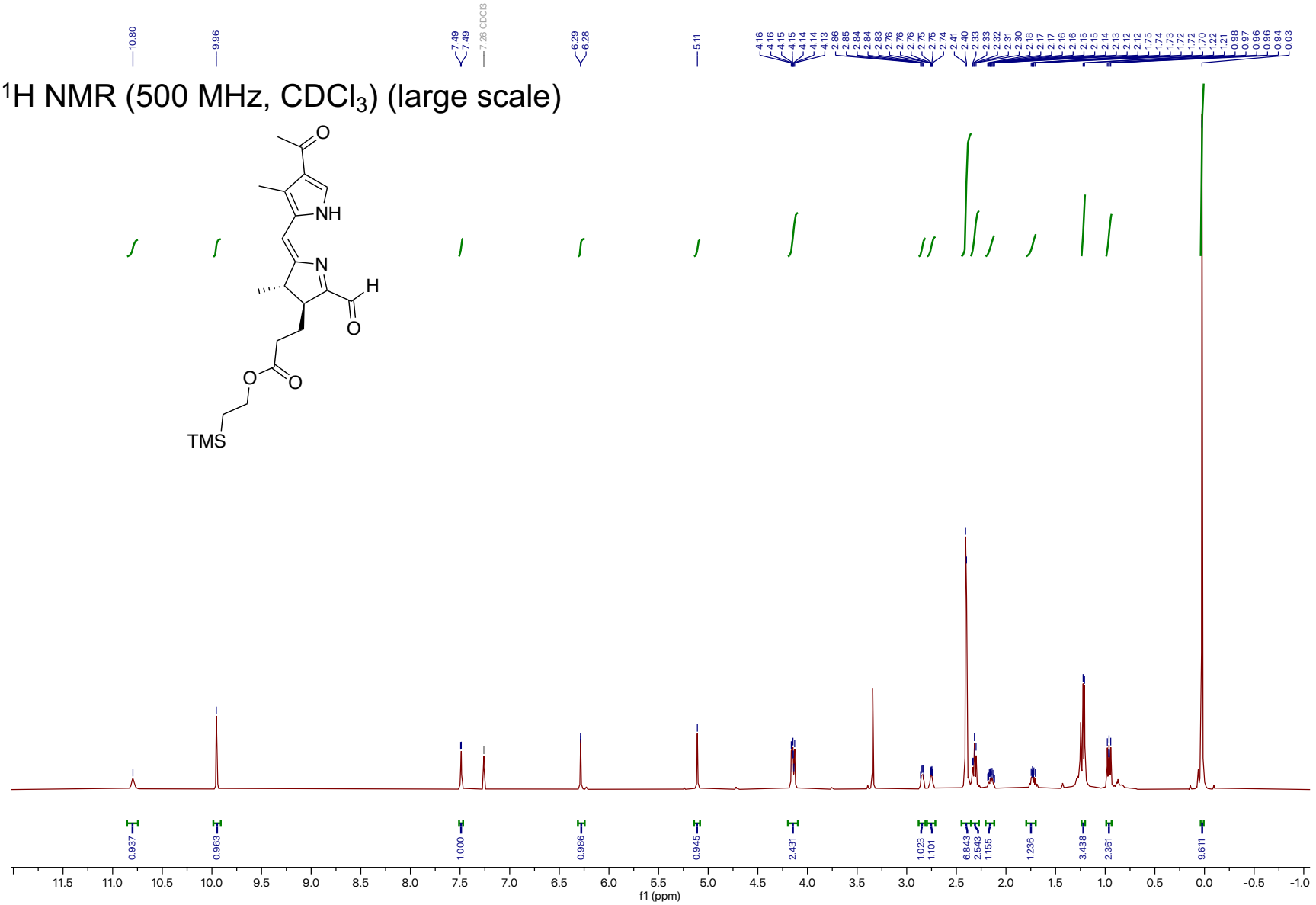

194.64
182.34
173.07
154.93
129.16
125.76
124.36
118.75
104.57
41.90
31.72
27.92
26.91
21.33
17.45
10.79
-1.41
$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$)
O
NH
N
CH_2OH
O
O
TMS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


1H NMR (700 MHz, CDCl3) (small scale)
O
NH
N
H
O
O
O
TMS
10.80
9.96
7.50
7.49
6.29
5.11
4.16
4.16
4.15
4.15
4.14
2.86
2.85
2.85
2.76
2.84
2.75
2.75
2.42
2.40
2.34
2.33
2.33
2.32
2.32
2.32
2.31
2.17
2.16
2.16
2.15
1.76
1.75
1.75
1.74
1.73
1.73
1.73
1.72
1.71
1.70
1.23
1.22
0.98
0.97
0.97
0.97
0.96
0.03
1.211
0.834
1.000
1.193
1.415
1.994
1.230
1.316
5.477
1.810
1.402
1.390
2.987
1.959
8.818
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

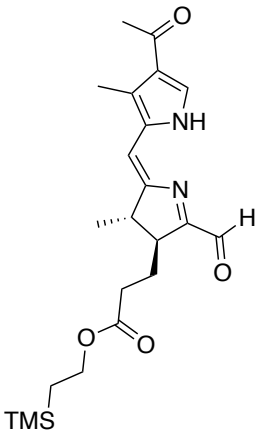
$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$) (small scale)

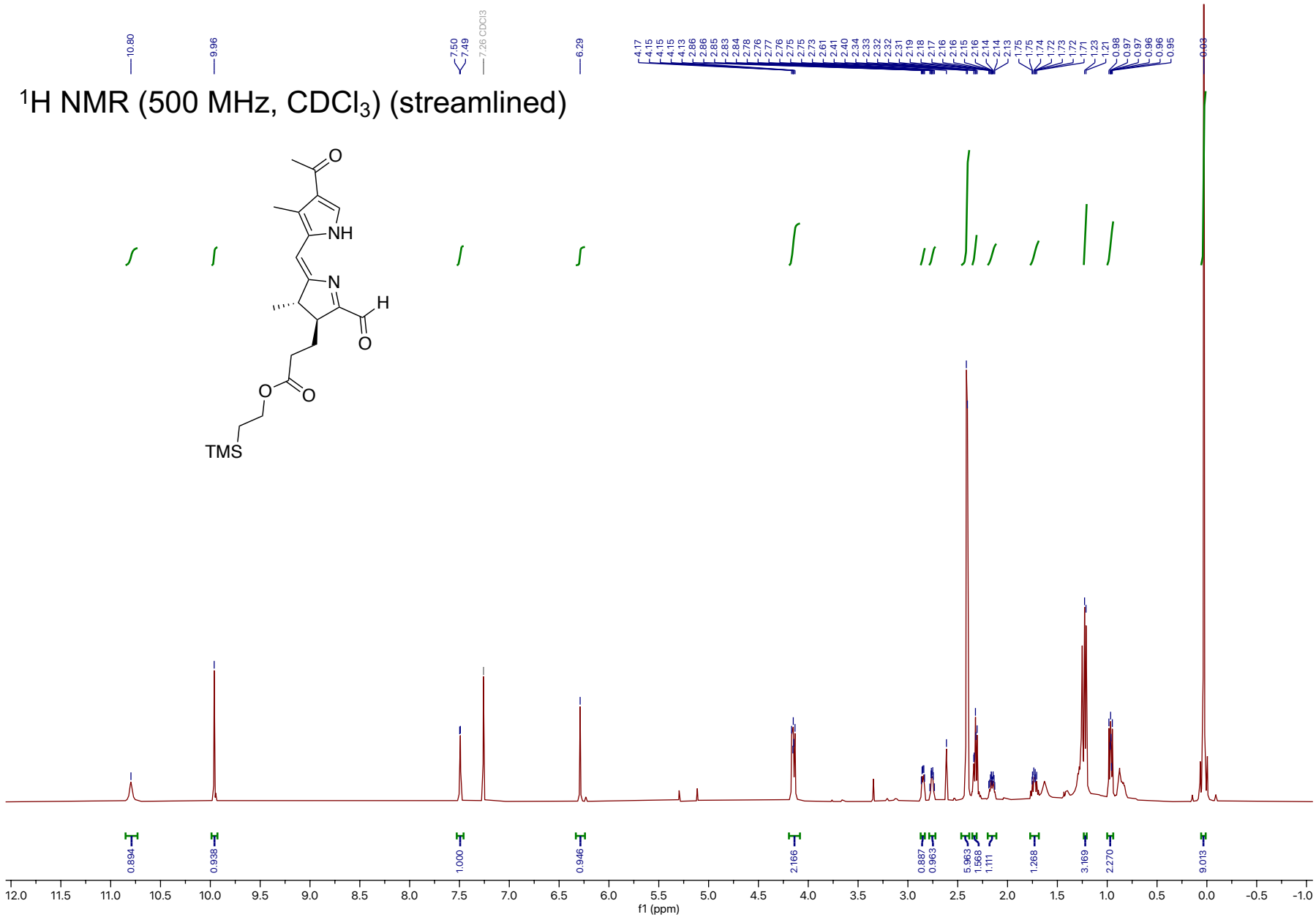


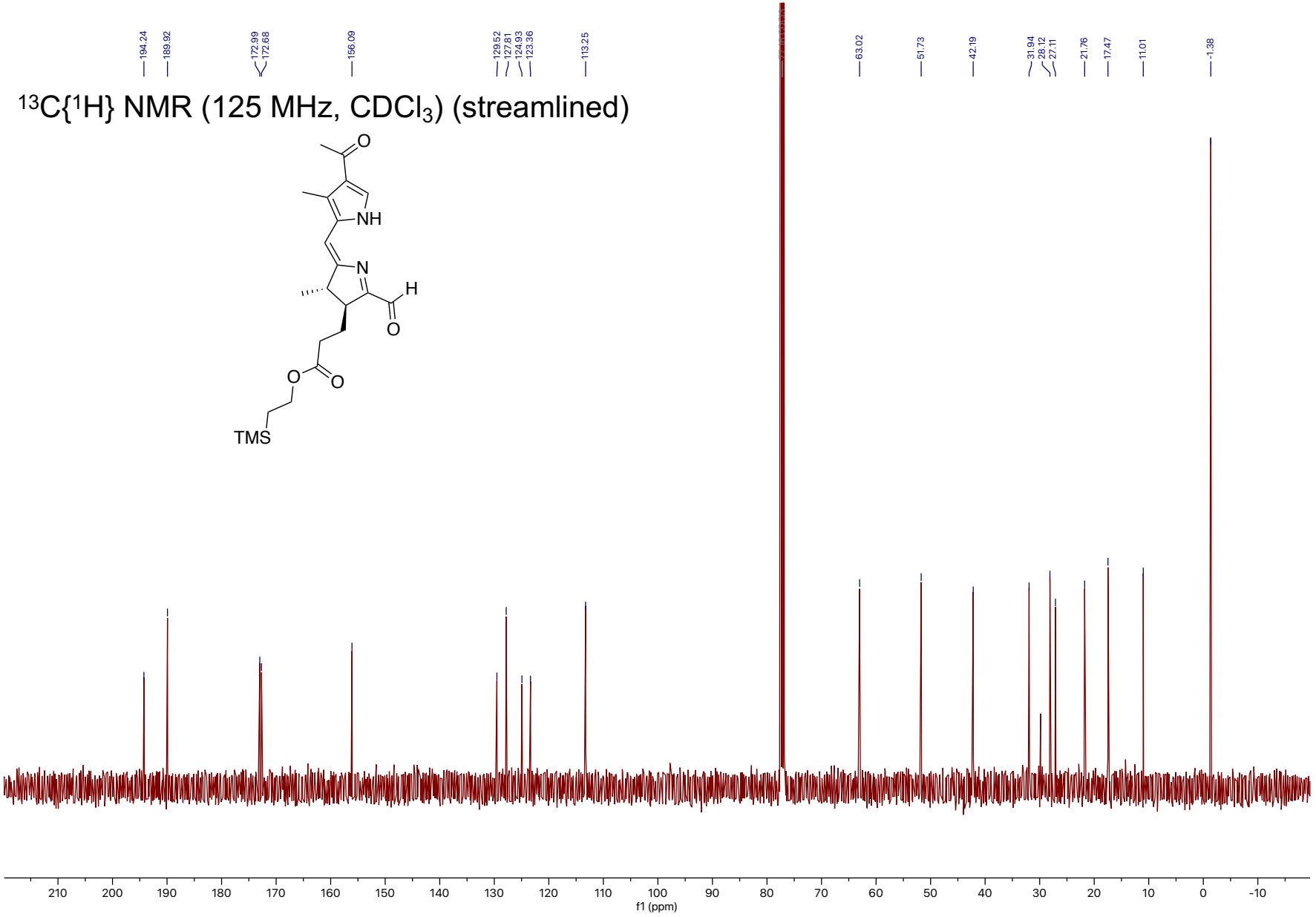
^{1}H NMR (500 MHz, $CDCl_3$) (large scale)

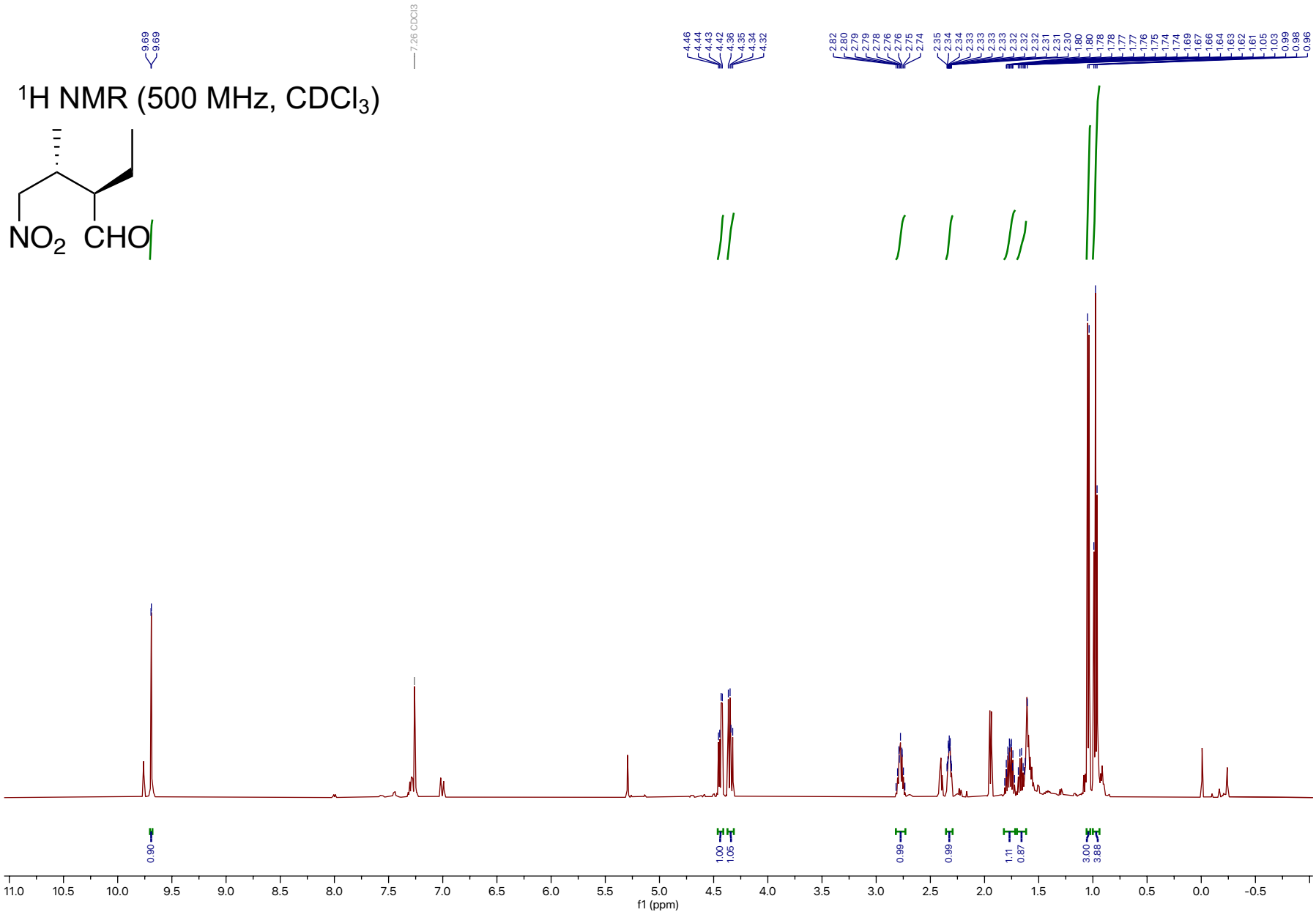


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) (large scale)

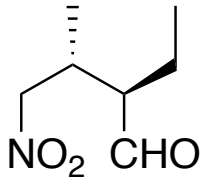



^{1}H NMR (500 MHz, $CDCl_3$) (streamlined)
10.80
9.96
7.50
7.49
7.26 CDCl3
6.29
0.93
NH
N
H
O
O
O
O
TMS
0.894
0.938
1.000
0.946
2.166
0.887
0.963
5.963
1.568
1.111
1.268
3.169
2.270
9.013
f1 (ppm)

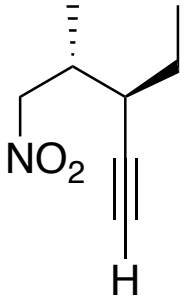

194.24
189.92
172.99
172.68
156.09
129.52
127.81
124.93
123.36
113.25
63.02
51.73
42.19
31.94
28.12
27.11
21.76
17.47
11.01
-1.38
13C{1H} NMR (125 MHz, CDCl3) (streamlined)
O
NH
N
H
O
O
O
TMS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
NO_2 CHO
9.69
9.69
7.26 CDCl3
4.46
4.44
4.43
4.42
4.36
4.35
4.34
4.32
2.82
2.80
2.79
2.79
2.78
2.76
2.76
2.75
2.74
2.35
2.34
2.34
2.33
2.33
2.33
2.32
2.32
2.32
2.31
2.31
2.30
1.80
1.80
1.78
1.78
1.77
1.77
1.76
1.75
1.74
1.74
1.69
1.67
1.66
1.64
1.63
1.62
1.61
1.05
1.03
0.99
0.98
0.96
0.90
1.00
1.05
0.99
0.99
1.11
0.87
3.00
3.88
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

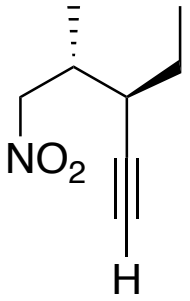
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



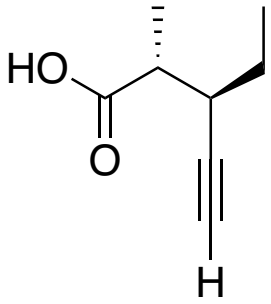
^{1}H NMR (500 MHz, $CDCl_3$)



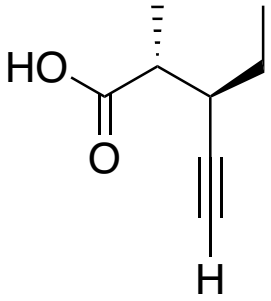
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



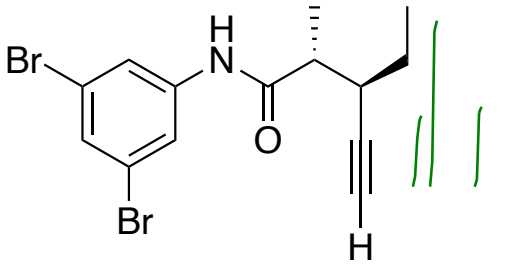
^{1}H NMR (500 MHz, $CDCl_3$)



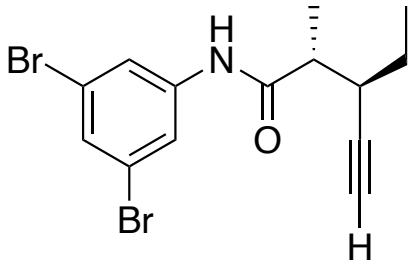
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



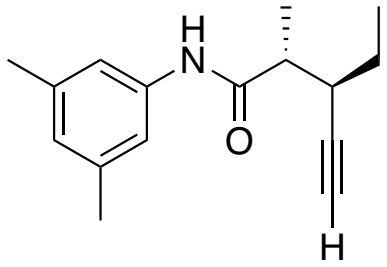
^{1}H NMR (500 MHz, $CDCl_3$)



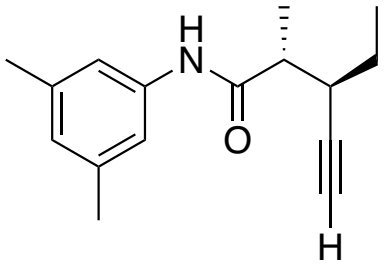
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



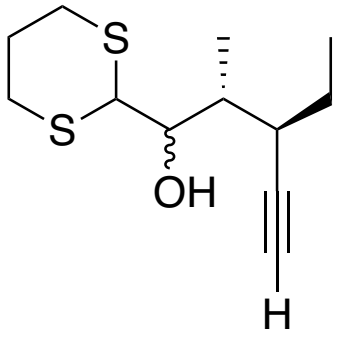
^{1}H NMR (500 MHz, $CDCl_3$)



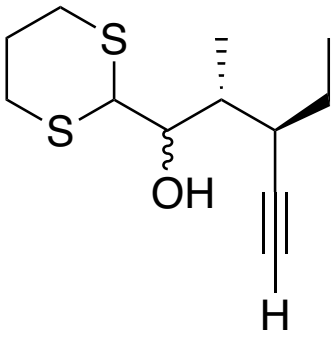
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



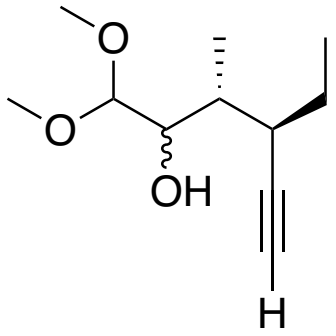
^{1}H NMR (500 MHz, $CDCl_3$)



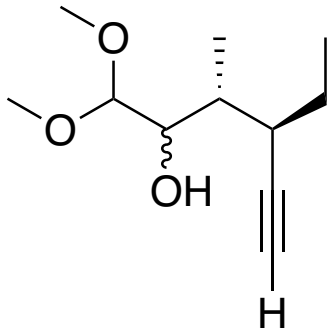
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



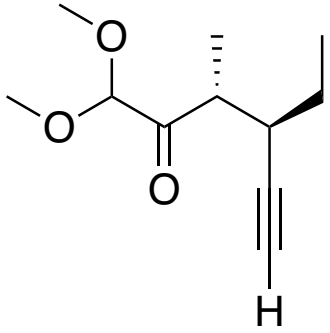
^{1}H NMR (500 MHz, $CDCl_3$)



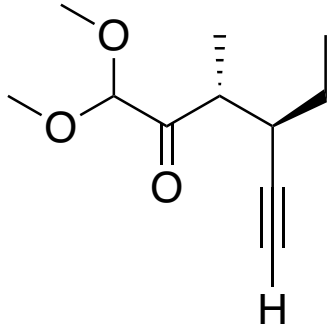
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



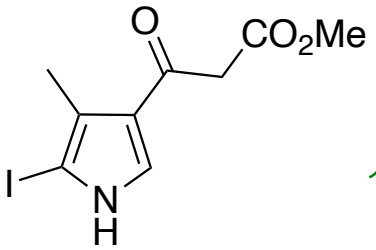
^{1}H NMR (500 MHz, $CDCl_3$)



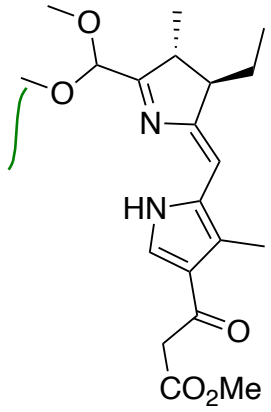
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$)



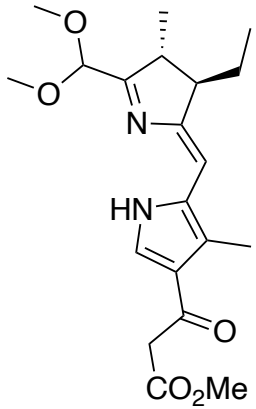
^{1}H NMR (500 MHz, $CDCl_3$)

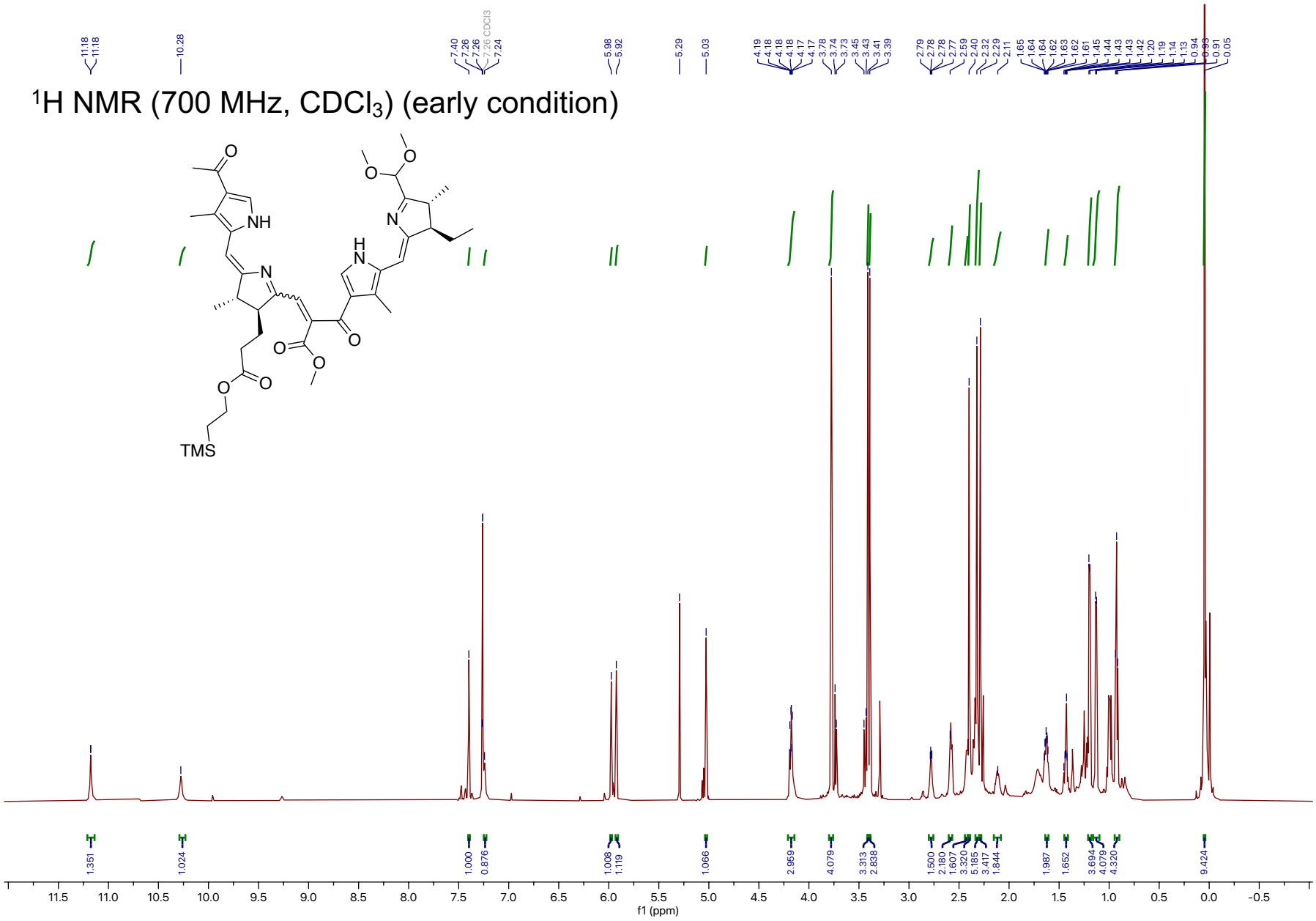


^{1}H NMR (700 MHz, $CDCl_3$)

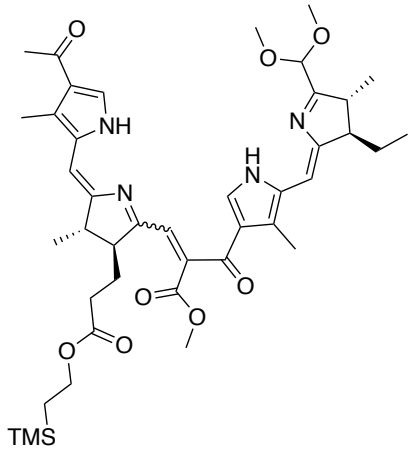


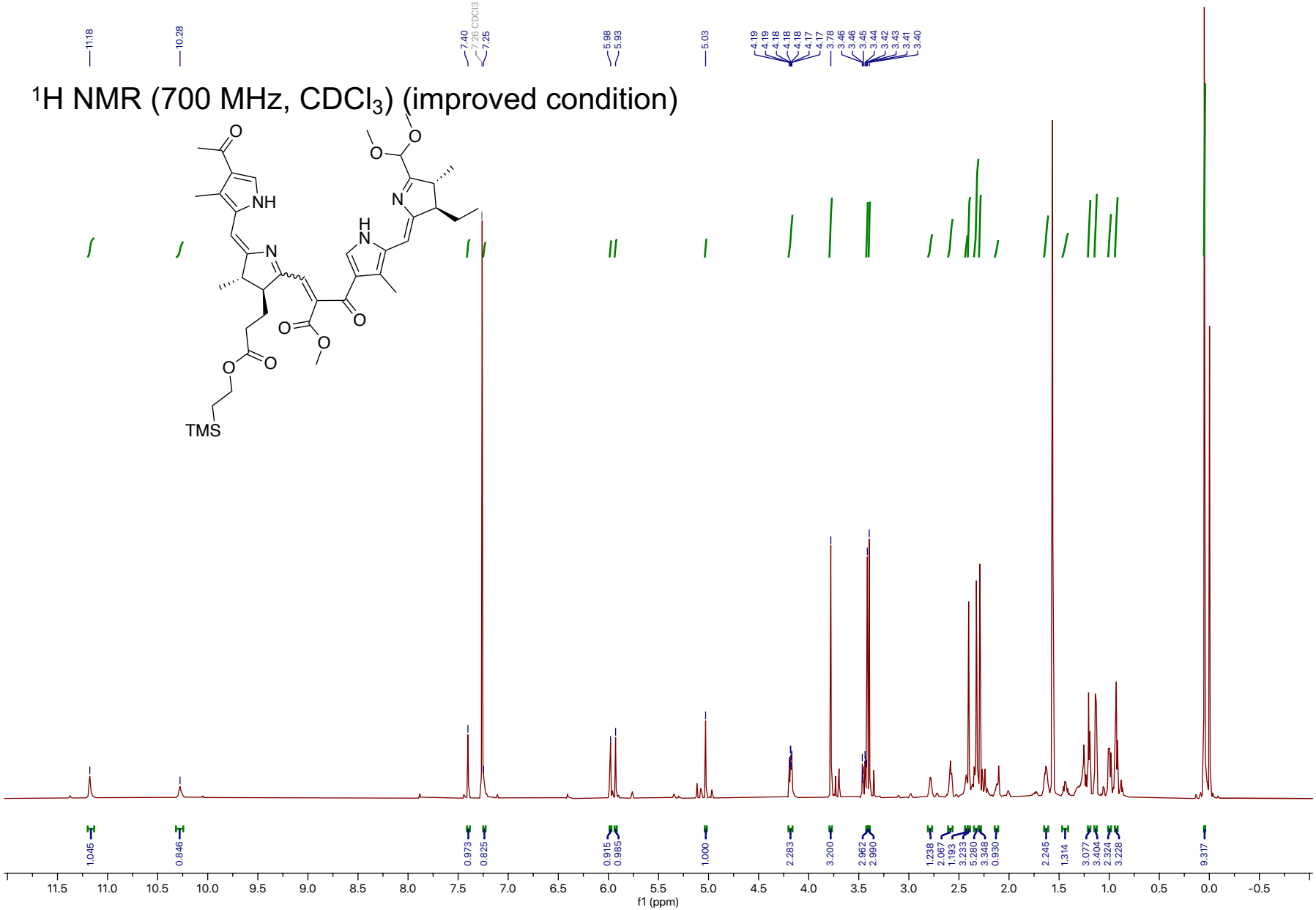
$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$)



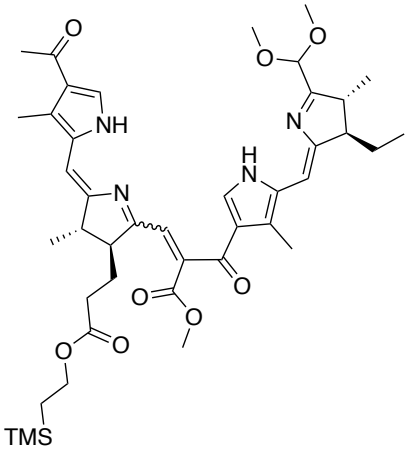

^{1}H NMR (700 MHz, $CDCl_3$) (early condition)
TMS
f1 (ppm)

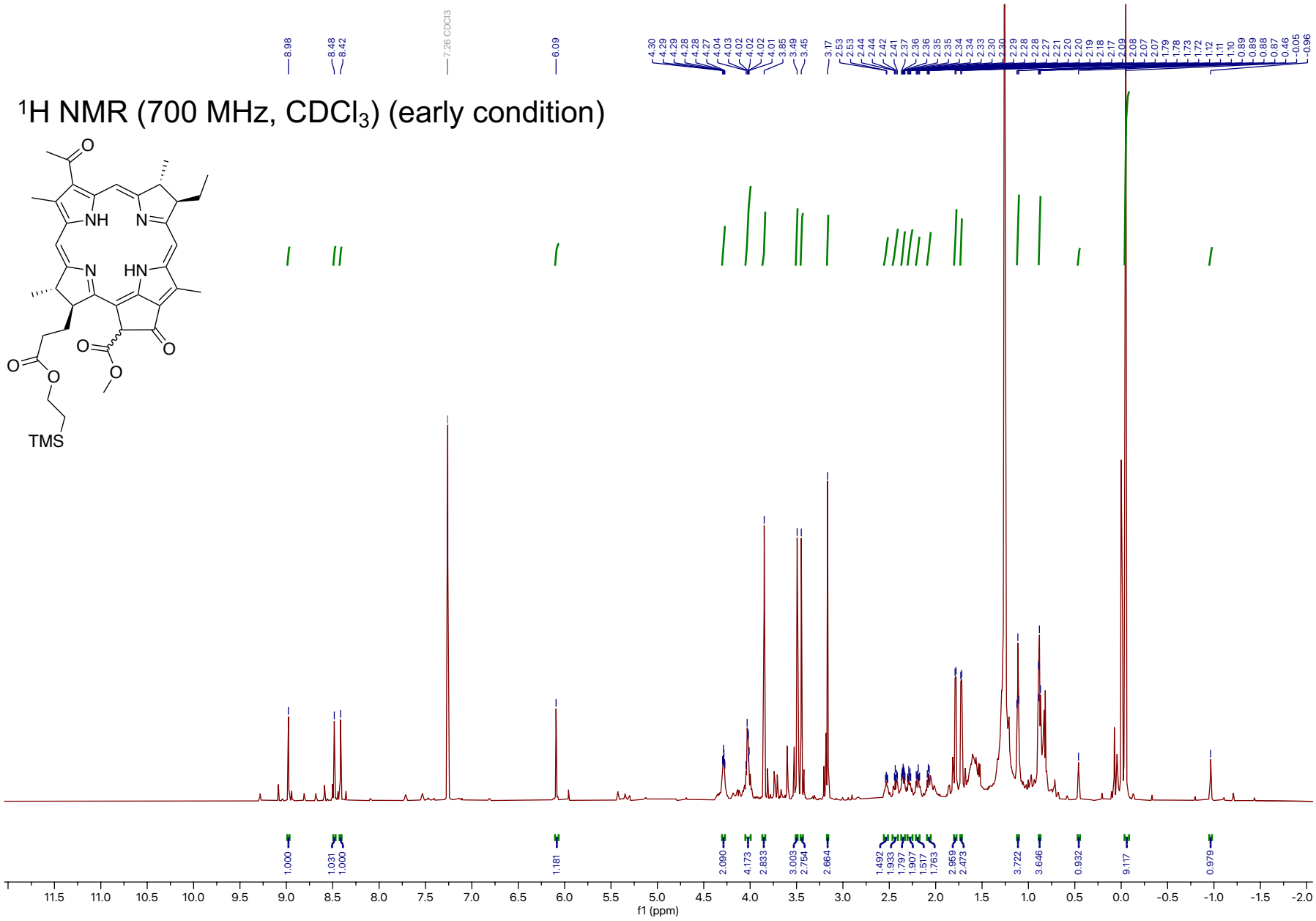
$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$) (early condition)

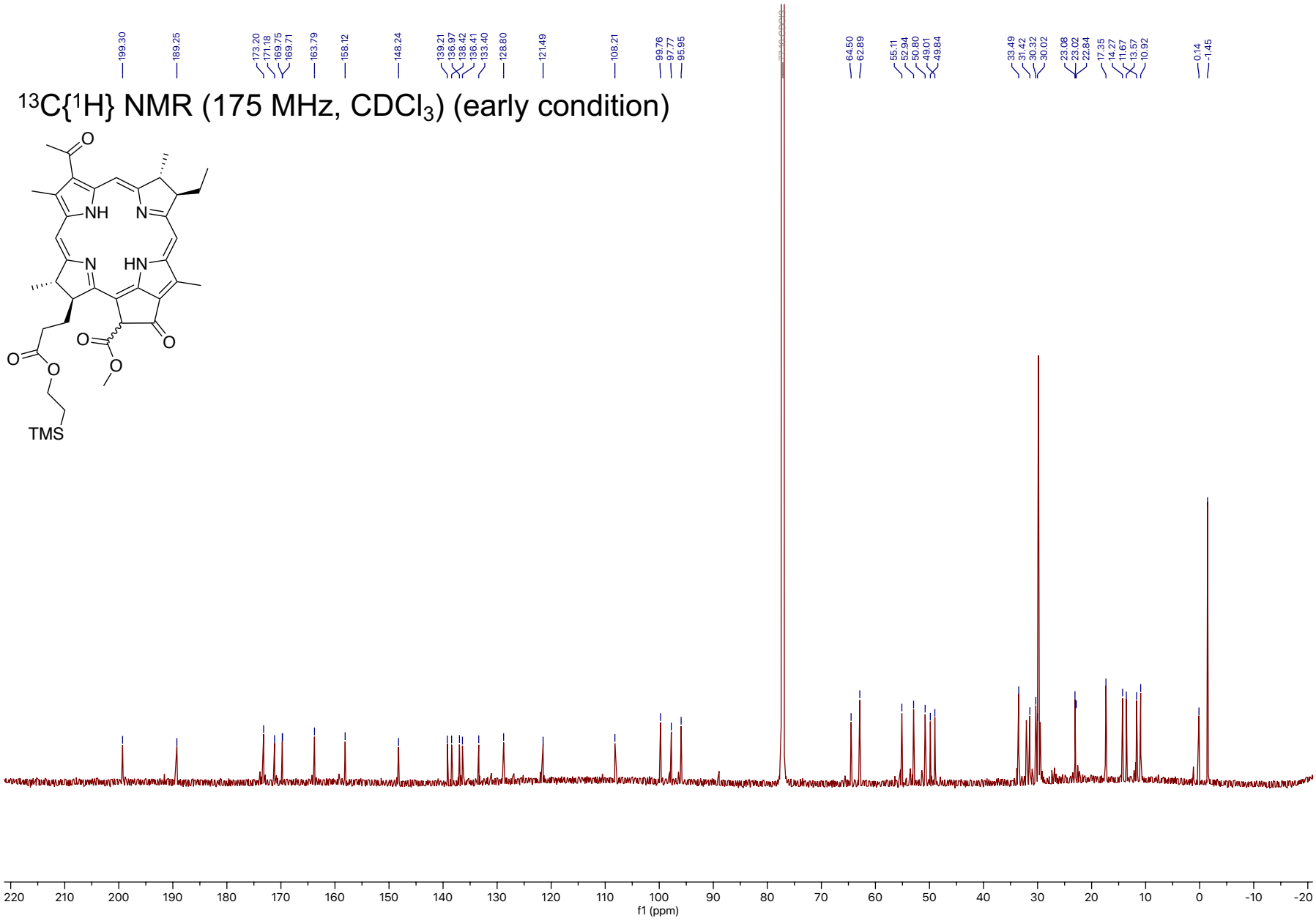


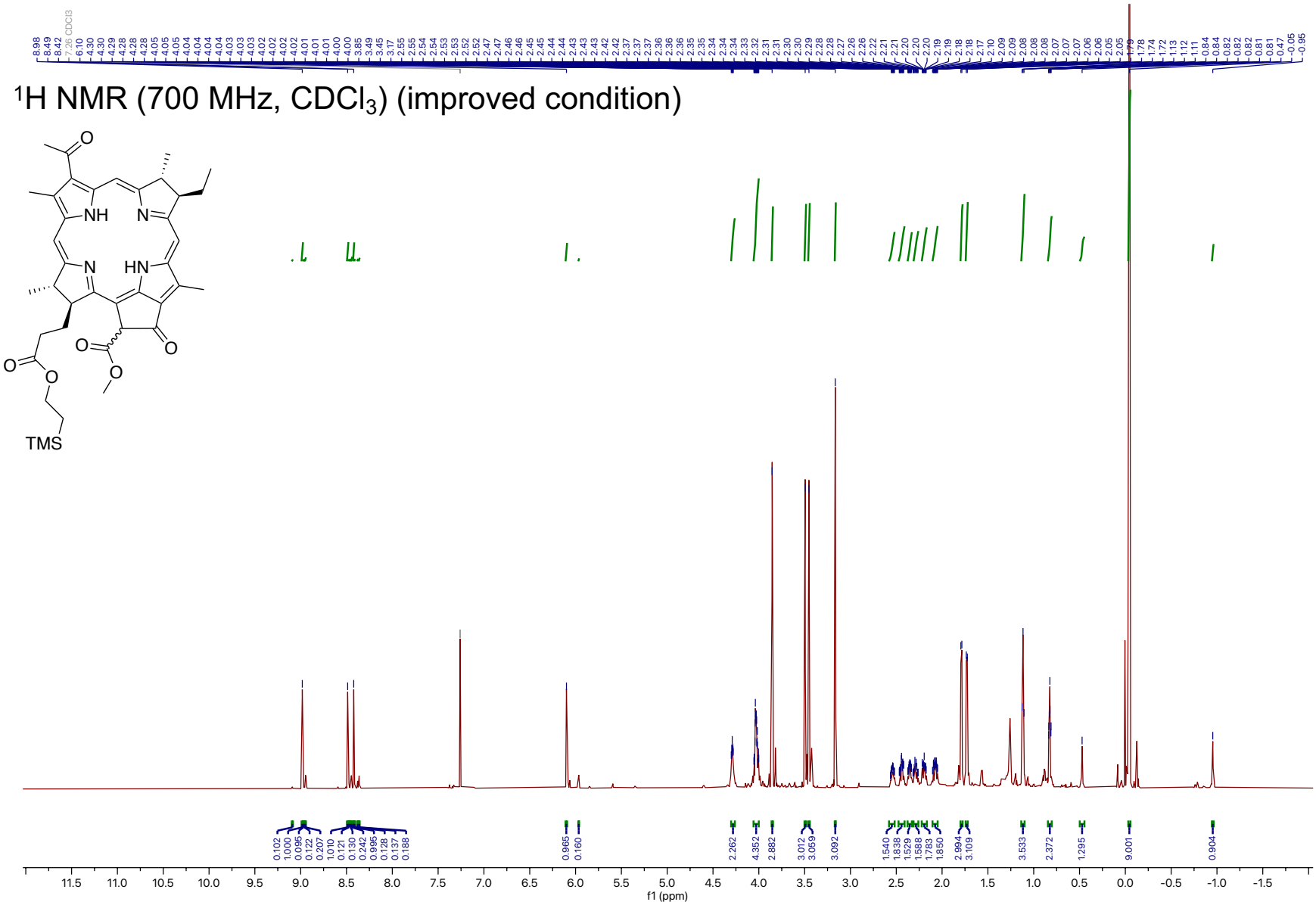

^{1}H NMR (700 MHz, $CDCl_3$) (improved condition)
TMS
f1 (ppm)

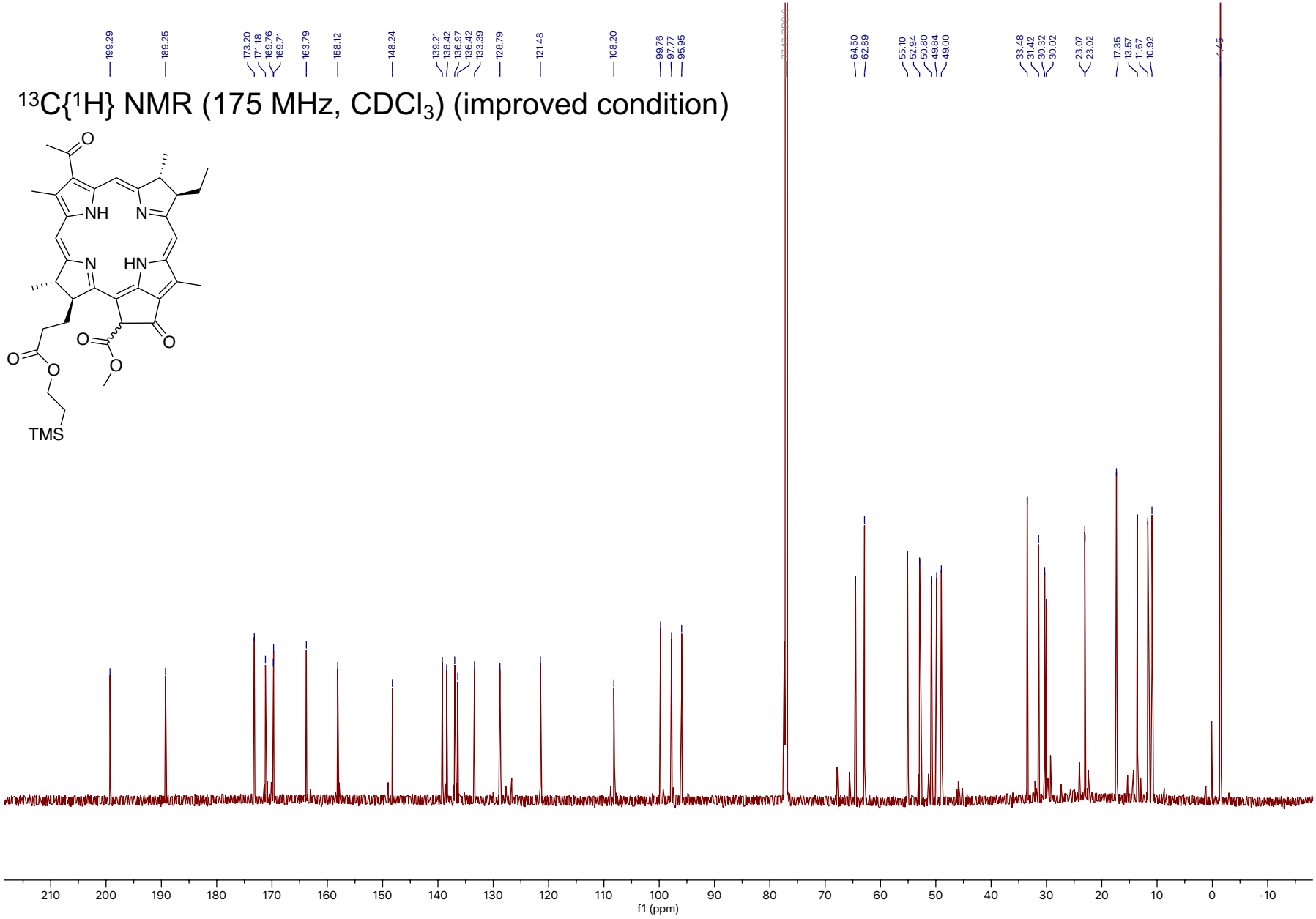
$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$) (improved condition)



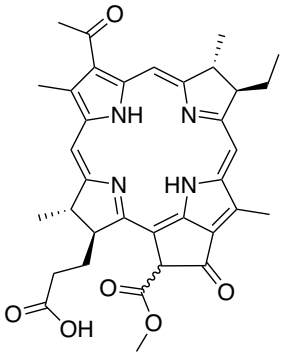

^{1}H NMR (700 MHz, $CDCl_3$) (early condition)
TMS
f1 (ppm)


199.30
189.25
173.20
171.18
169.75
169.71
163.79
158.12
148.24
139.21
136.97
138.42
136.41
133.40
128.80
121.49
108.21
99.76
97.77
95.95
64.50
62.89
55.11
52.94
50.80
49.01
49.84
33.49
31.42
30.32
30.02
23.08
23.02
22.84
17.35
14.27
11.67
13.57
10.92
0.14
-1.45
13C{1H} NMR (175 MHz, CDCl3) (early condition)
NH
N
N
HN
O
O
O
O
O
O
TMS
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

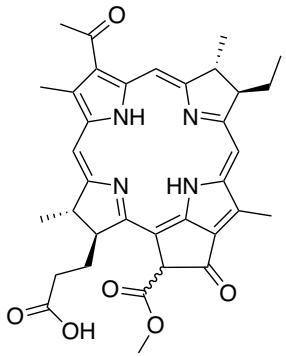

^{1}H NMR (700 MHz, $CDCl_3$) (improved condition)
NH
N
N
HN
O
O
O
O
O
O
TMS
f1 (ppm)


199.29
189.25
173.20
171.18
169.76
169.71
163.79
158.12
148.24
139.21
138.42
136.97
136.42
133.39
128.79
121.48
108.20
99.76
97.77
95.95
64.50
62.89
55.10
52.94
50.80
49.84
49.00
33.48
31.42
30.32
30.02
23.07
23.02
17.35
13.57
11.67
10.92
1.45
13C{1H} NMR (175 MHz, CDCl3) (improved condition)
NH
N
N
HN
O
O
O
O
O
O
TMS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

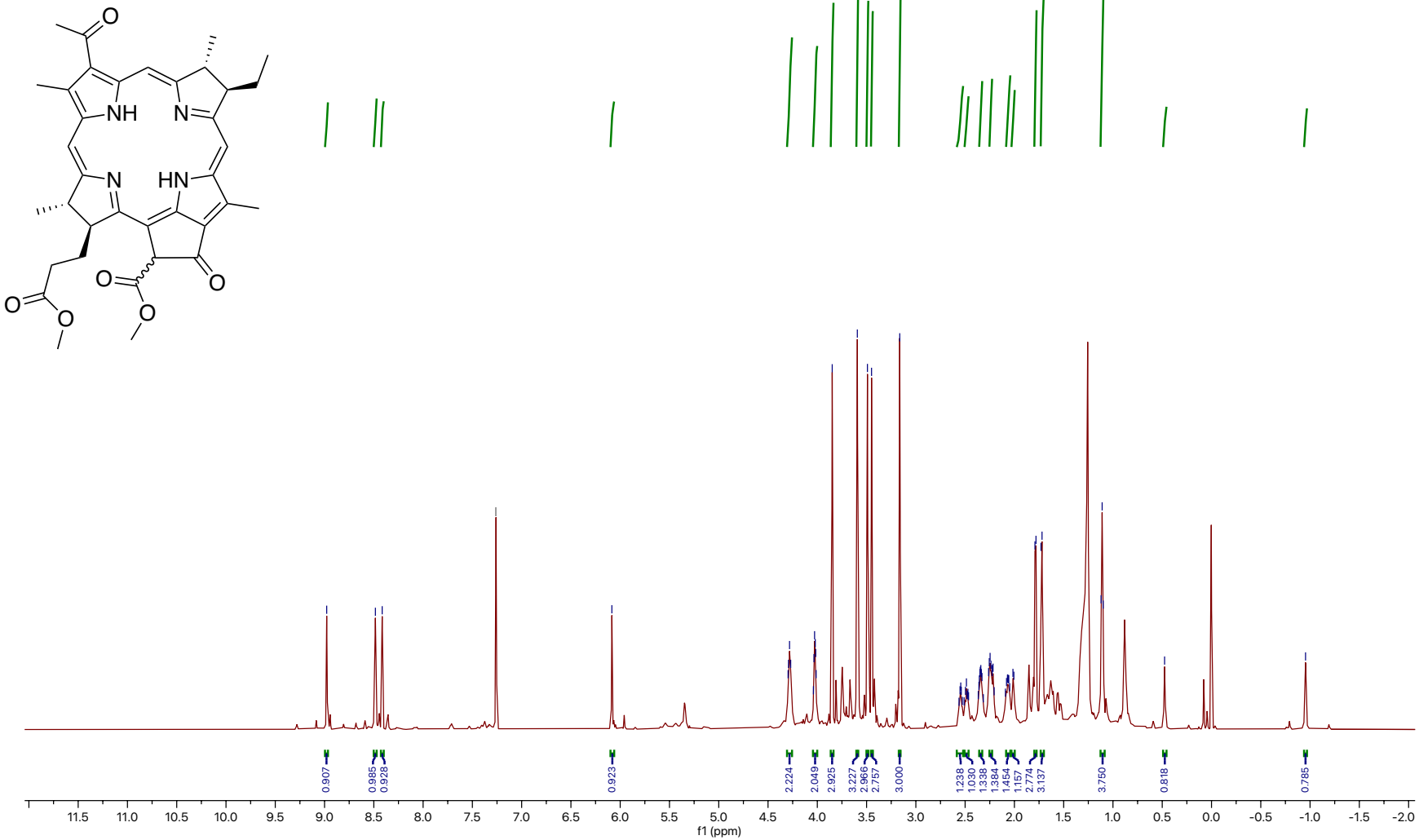
^{1}H NMR (600 MHz, $CDCl_3$) (improved condition)



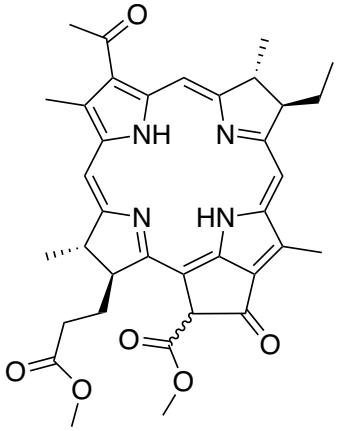
$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) (improved condition)

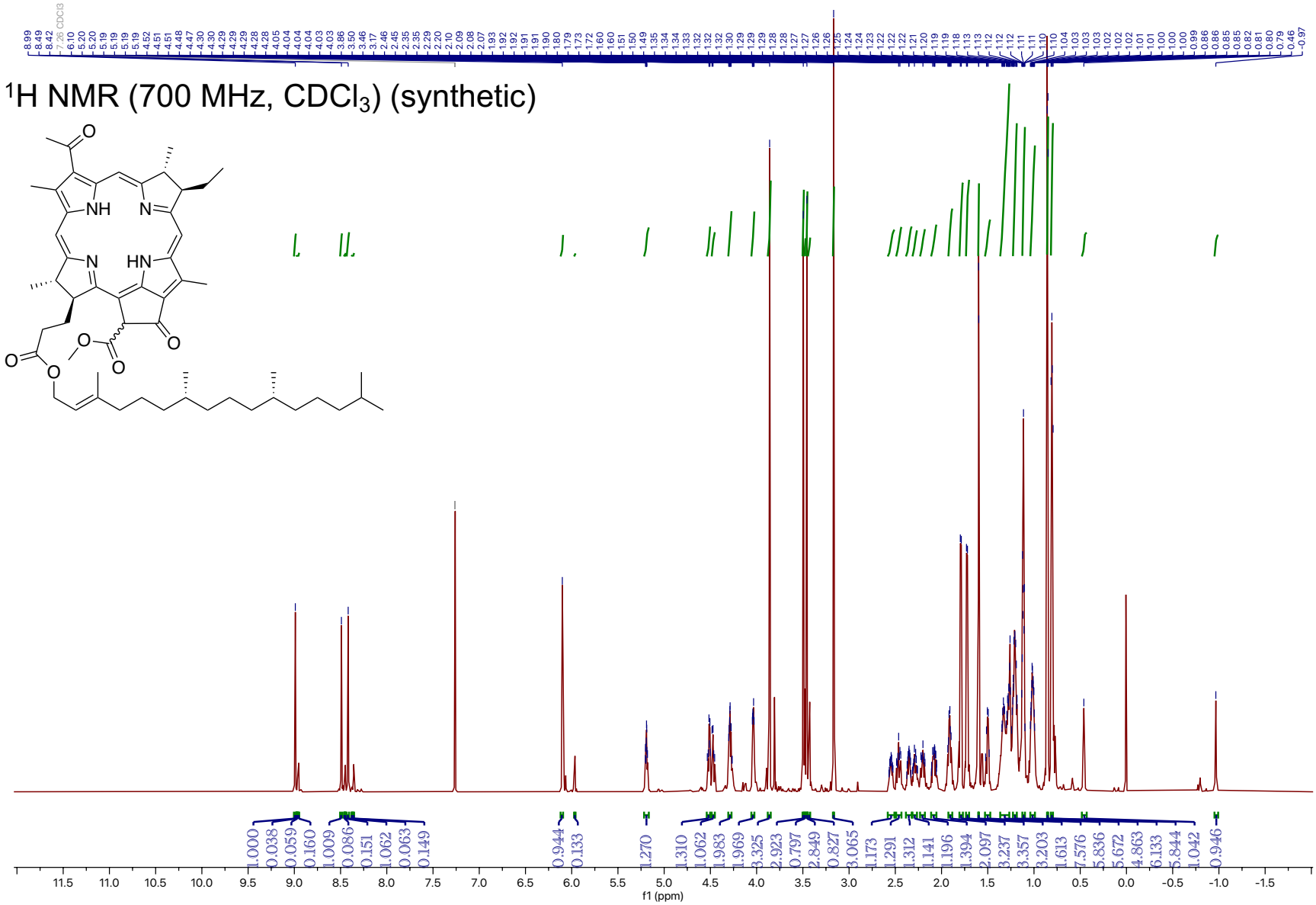


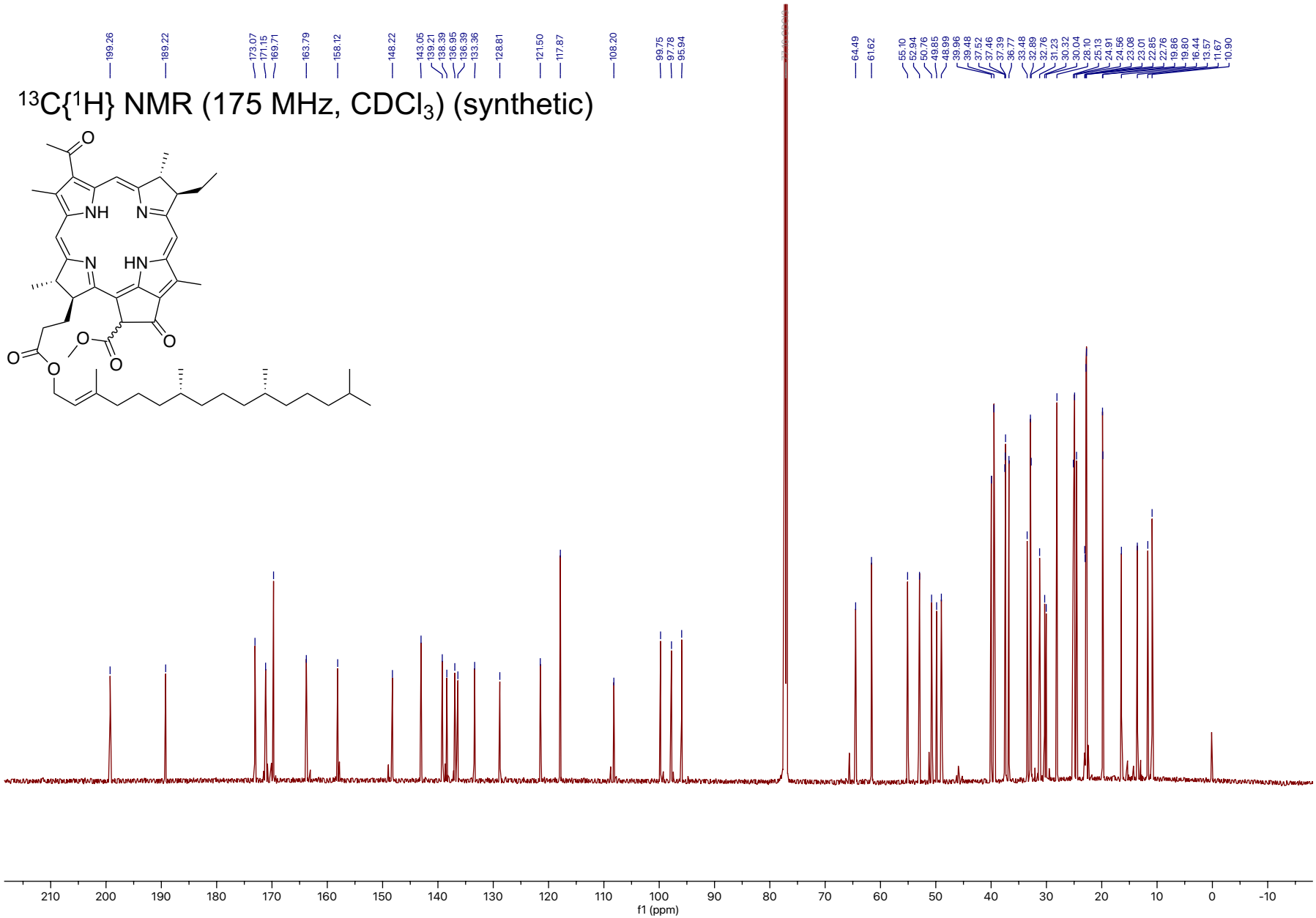
^{1}H NMR (700 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$)




^{1}H NMR (700 MHz, $CDCl_3$) (synthetic)
f1 (ppm)


199.26
189.22
173.07
171.15
169.71
163.79
158.12
148.22
143.05
139.21
138.39
136.95
136.39
133.36
128.81
121.50
117.87
108.20
99.75
97.78
95.94
64.49
61.62
55.10
52.94
50.76
49.85
48.99
39.96
39.48
37.52
37.46
37.39
36.77
33.48
32.89
32.76
31.23
30.32
30.04
28.10
25.13
24.91
24.56
23.08
23.01
22.85
22.76
19.86
19.80
16.44
13.57
11.67
10.90
13C{1H} NMR (175 MHz, CDCl3) (synthetic)
NH
N
N
HN
O
O
O
O
O
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)